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i. Motility of the Human Esophagus in Control Subjects and in Patients with Esophageal Disorders PHILIP KRAMER AND FRANZ J. INGELFINGER 168

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These balloon-kymographic studies of esophageal motility in normal subjects and in diseases affecting the esophagus yielded patterns of both physiologic and clinical interest. The results in cardiospasm throw new light on the causes and mechanisms of that disorder.

Treatment of Chronic Non-specific Ulcerative Colitis with Aureomycin. A Preliminary Report JEROME A. MARKS, LOUIS T. WRIGHT AND SELIG STRAX 180

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Chronic gastritis has been shown by gastroscopic methods to be a common disorder but it remains of obscure and controversial significance. The results of this study contradict recent tendencies to ascribe definite symptom patterns to the several types of chronic gastritis.

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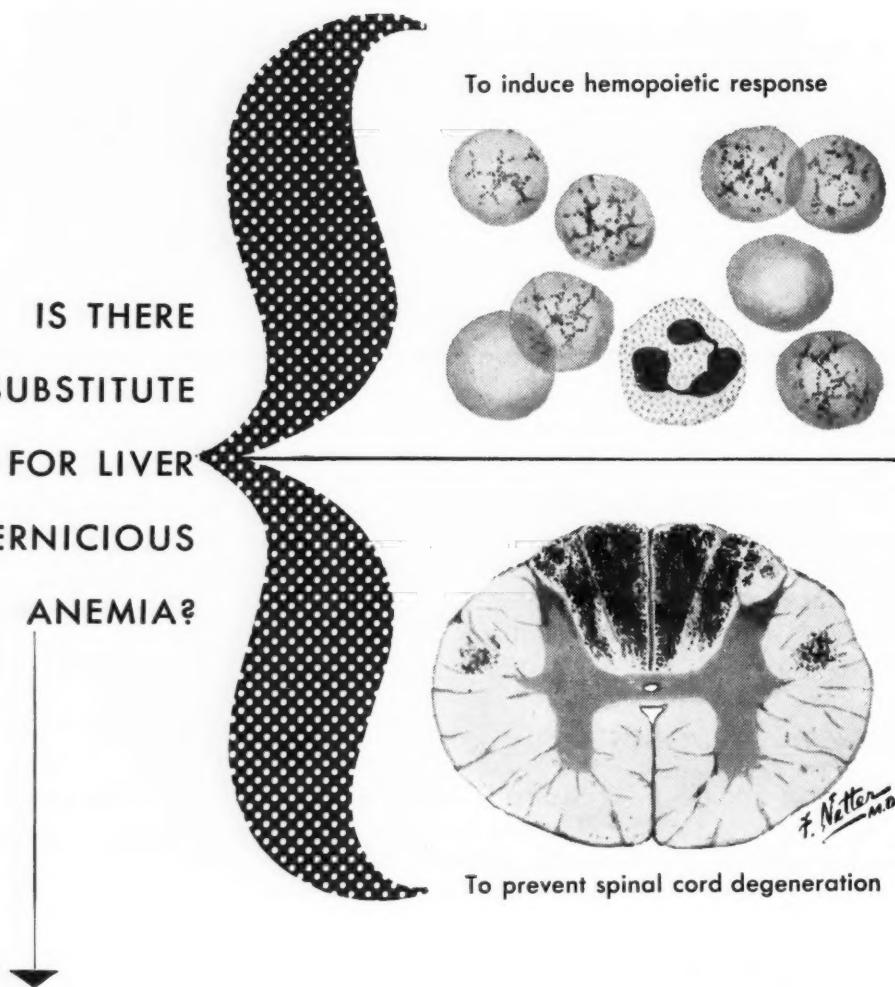
Clinico-pathologic Conferences (Washington University School of Medicine)—A complex clinical problem, discussion of which is carried out by fourth-year medical students as a teaching exercise—and they do very well indeed.

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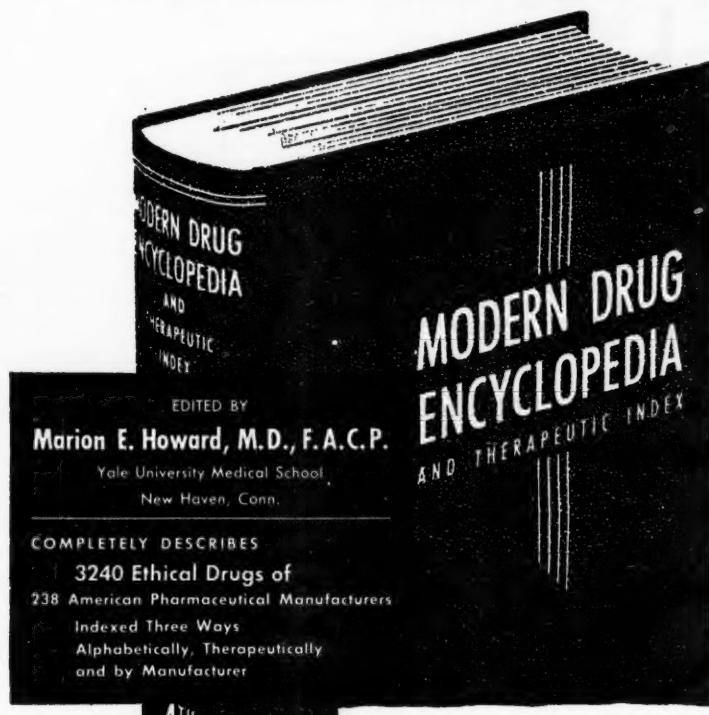
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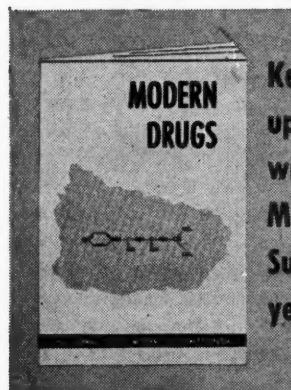
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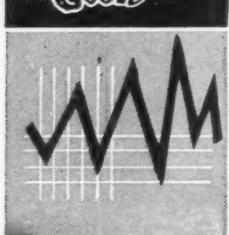
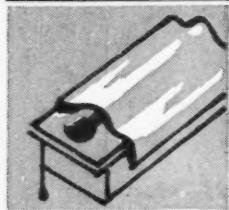
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2. Gastineau, C. F.; Rynearson, E. H., and Irmisch, A. K.: Treatment of the Fat and Lean, *J.A.M.A.* 139:86 (Jan. 8) 1949.
3. Elvehjem, C. A.: The Vitamin B Complex, *Council Reports, J.A.M.A.* 138:960 (Nov. 27) 1948.

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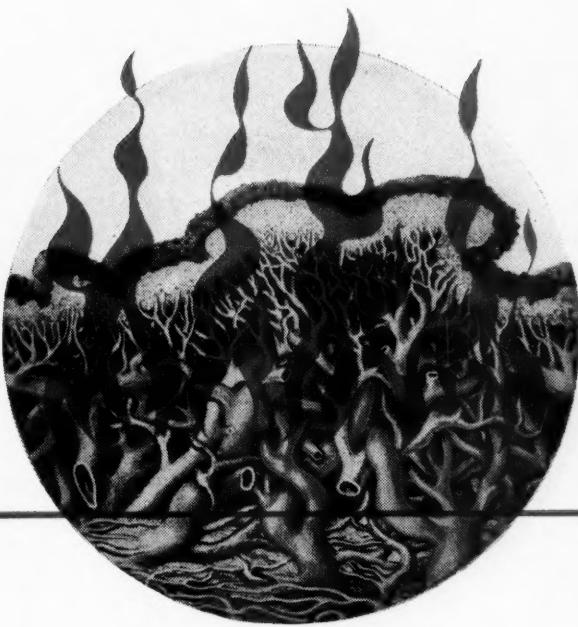
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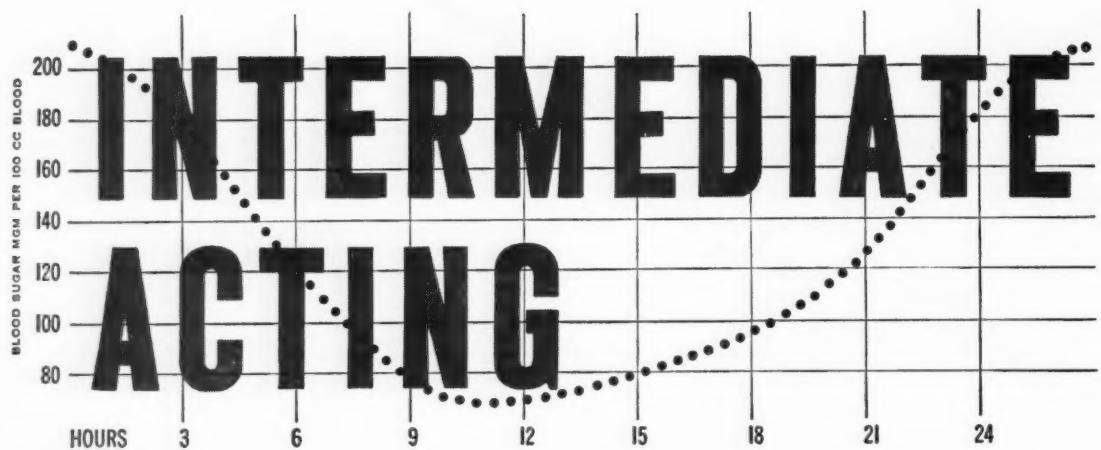
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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.



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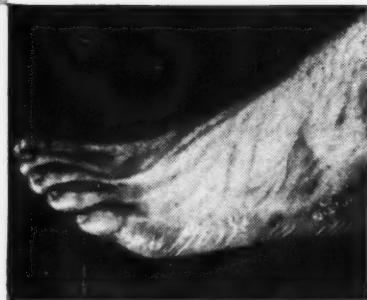
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REFERENCES: 1. McGavack, T. H. and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9:61, 1946.
2. Weissberg, J., McGavack, T. H. and Boyd, Linn J.: Am. J. Digest. Dis., 15:332, 1948.

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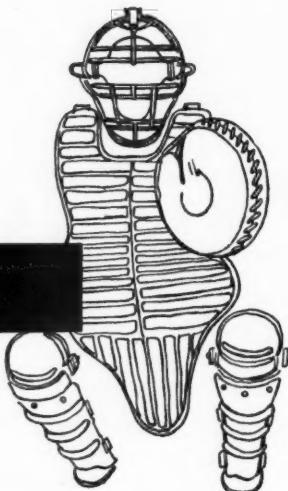
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Editorial

Vagotomy for Peptic Ulcer

INTERNISTS as well as surgeons have recently become deeply concerned about the place of bilateral vagotomy in the management of patients with refractory peptic ulcer. Physiologists for more than fifty years have been aware of the depressant effects of vagotomy on the secretory and motor functions of the stomach and more recently on the secretory function of the pancreas. But although Latarjet in 1922 included this procedure along with gastro-enterostomy in six patients with peptic ulcer, with good temporary results in five, it was not until 1943 that its application in man received special attention. In that year Dragstedt and Owens¹ reported good results from transthoracic vagotomy in two patients with duodenal ulcer. Following their lead many other surgeons have adopted the procedure, with or without accompanying gastric surgery, and have confirmed the original observations as to relief of pain, reduction in gastric acidity and, in most instances, healing of the ulcer. More recently most surgeons in order to investigate the stomach directly have accomplished the procedure subdiaphragmatically. This has permitted them at the same time to perform a gastro-enterostomy, gastrectomy or pyloroplasty; some of them adding gastric surgery only when an obstruction was found, but others, whether or not obstruction was demonstrable, in an attempt to prevent the gastric retention that so commonly follows vagal section.

¹ DRAGSTEDT, L. R. and OWENS, F. M. Supradiaaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proc. Soc. Exper. Biol. & Med.*, 53: 152, 1943.

Many thousands of patients with peptic ulcer have now been subjected to vagotomy, with or without gastric surgery, and apparently with satisfactory results in most instances. It should be appreciated, however, that as yet the duration of postoperative observation of these patients is relatively short and that many therapeutic procedures received with equal enthusiasm have subsequently been abandoned, or at least restricted in their application, because of ultimate complications. One cannot but wonder, therefore, if the time has not come to abandon temporarily the ready employment of vagotomy until a longer period of evaluation of results is available. This would seem especially indicated in view of the data available in the physiologic literature and of the frequent reports of unsatisfactory results that are already appearing in the clinical literature.

In the late nineteenth century Pavlov² demonstrated that dogs subjected to complete vagotomy developed stagnation in the stomach leading to death. Thomas and Komorov³ on the basis of animal work regard complete section of the vagi as incompatible with life and explain long survival after the modern operation in man on the basis of incompleteness of the section. Crider and Thomas⁴ have also shown that after vagotomy the output of pancreatic enzymes is reduced by 50 per cent or more.

² PAVLOV, I. P.³

³ THOMAS, J. E. and KOMOROV, S. A. Physiological aspects of vagotomy. *Gastroenterology*, 11: 413, 1948.

⁴ CRIDER, J. O. and THOMAS, J. E. Secretion of pancreatic juice after cutting extrinsic nerves. *Am. J. Physiol.*, 141: 730, 1944.

Vansant⁵ has maintained that the depression of secretion produced by vagotomy in the dog is transitory, the acidity returning to a normal level after two or three years. All workers agree as to the depression of the motor function of the stomach, some reporting prolonged troublesome atony with almost complete absence of hunger contractions. Indeed the relief of pain almost invariably reported is presumably due to a lack of tonicity of the gastric wall.

The available reports on the results of the clinical application of vagotomy are confusing because of uncertainty as to the degree of completeness of the division of the nerve fibers and because of the other operative procedures so commonly associated with it. The insulin test of Hollander designed to determine whether or not vagal section is complete has not proved entirely satisfactory, and as yet no other method has been advanced. Some patients have previously had a subtotal gastric resection or gastro-enterostomy, some have had such an operation simultaneously and some, because of gastric retention, soon afterward. Without attempting to classify the cases one gets the impression from the clinical literature that in spite of ulcer pain relief, many of the patients, at least for months, are quite uncomfortable and certainly in some there is a failure to heal, or they develop a recurrent ulcer. Even though some type of gastro-enterostomy also is accomplished, gastric retention with a peculiar sense of fullness and sometimes vomiting often persists for a long time. Eleven of Grimson's⁶ thirty-six patients had had a previous gastro-enterostomy, five had such an operation at the time of vagotomy and five required it subsequently; yet twenty-eight had post-prandial distress for at least three months, two developed hematemesis and one after twelve months had a new ulcer. Walters,⁷

⁵ VANSANT, F. R. Late effect of section of vagus nerves on gastric acidity. *Proc. Staff Meet., Mayo Clin.* 6: 576, 1931.

⁶ GRIMSON, K. S. Clinical evaluation of complications observed after transthoracic vagotomy. *Arch. Surg.*, 55: 175, 1947.

⁷ WALTERS, W. Gastric neurectomy. *Arch. Surg.*, 55: 151, 1947.

in a series of eighty-three vagotomized patients at the Mayo Clinic, subsequently found one perforation, eight recurrent or persistent ulcers, and eight with troublesome gastric or intestinal stasis, including one operated upon for suspected intestinal obstruction (i.e., poor results in 20 per cent). He states that Colp in thirty-three patients had only eighteen whom he regarded as cured and one who subsequently had a perforation. Johns and Grose⁸ in forty-one carefully followed patients had seven unsatisfactory results: three from ulcer recurrence and four from gastric retention. Four of their patients required re-operation (although in three no obstruction was found) and two had subsequent hemorrhage. Of their seven failures, four obtained eventual relief from gastroenterostomy but two did not. In the total series they obtained unsatisfactory results in 17 per cent (27 per cent of those having had vagotomy alone). Thirteen of Moore's⁹ 116 patients developed a recurrence, eleven of them eventually recovering on a medical program and only one requiring subsequent subtotal gastric resection. Wilkinson and Sullivan,¹⁰ in parallel series, respectively, with gastrectomy alone and with gastrectomy plus vagotomy, found an equal recurrence rate but slightly better satisfaction on the part of the patient when only gastrectomy was done.

Medical management of the refractory peptic ulcer patient is admittedly unsatisfactory. To date the most consistently good results have followed subtotal gastrectomy. Although in some instances secondary ulceration, anemia or a nutritional disturbance follow, the effects of extensive gastrectomy in the previously unoperated patient have been satisfactory, both immediately and ultimately, in 85 to 95 per cent of the cases. They have been best when

⁸ JOHNS, T. N. P. and GROSE, W. E. Symposium on vagotomy in peptic ulcer: early surgical results in forty-three cases. *Bull. Johns Hopkins Hosp.*, 81: 92, 1947.

⁹ MOORE, F. O. Follow-up of vagotomy in duodenal ulcer. *Gastroenterology*, 11: 442, 1948.

¹⁰ WILKINSON, S. A. and SULLIVAN, J. C. Vagotomy combined with subtotal gastrectomy. *Gastroenterology*, 11: 457, 1948.

gastrectomy was done for gastric ulcer and worst when done on psychoneurotic patients with duodenal ulcers. Such results, therefore, may be regarded as a basis for comparison with those eventually obtained from vagotomy.

It may now be said that the immediate results of vagotomy are hardly so satisfactory as those of gastric resection. The relief of pain that usually results from vagotomy may in itself lead to a false sense of security, since in several instances it has masked a perforation. The depression of gastric motor function often accounts for a prolonged period of epigastric fullness and vomiting even when gastro-enterostomy also has been performed. As yet no assurance can be given that the previous gastric acidity will not recur. The ultimate effect of the operation on the pancreatic secretion is still in doubt. Secondary or associated gastric surgery is frequently necessary and, as is fully appreciated, when a stomal ulcer once develops (as it may after gastro-enterostomy) its management, even by

gastrectomy, leads to poor results. At any rate, vagotomy alone is usually contraindicated in gastric ulcer because of the difficulty in ruling out a malignant lesion.

On the other hand, vagotomy does seem to have found a place in the management of the marginal ulcer in which the other current operations often fail. Also it may be found useful in the psychoneurotic patient with a duodenal ulcer in whom gastrectomy now gives its poorest results. Indeed in the latter instance it may constitute a rational procedure because of the probability that in such a patient the mechanism of ulcer production depends primarily on a disturbance of the autonomic nervous system. Its place in the management of the ordinary duodenal ulcer patient, however, has not as yet been determined and, until further observations have been made on the patients already vagotomized, it would seem wise to exercise great caution in subjecting more patients with this type of ulcer to the operation.

T. GRIER MILLER, M.D.

Clinical Studies

Intubation Studies in Intestinal Allergy*

EUGENE M. SCHLOSS, M.D.

Philadelphia, Pennsylvania

IN the investigation of gastrointestinal allergy the principal modalities up to this time have involved a great variety of procedures including (1) methods of skin testing (scratch, intradermal and patch tests) for the presence of reagins; (2) clinical observations incident upon the use of elimination diets and, as a special adaptation of this method, the pulse rate study of Coca; (3) roentgenologic study of the effect of barium-specific food mixtures upon the tonus, motility and pattern of the several segments of the alimentary canal; (4) direct observation of local changes due to allergenic substances as seen through the gastro-scope or anoscope and (5) evaluation of alterations in the hematologic pattern, such as leukopenia, eosinophilia, etc., at certain intervals after the ingestion of suspected foods. Of these methods those dealing with skin testing are probably the least accurate; there is a notably high incidence of false reactions, both positive and negative;¹ in fact, the existence of a true reaction in the skin is a matter of conjecture except in those instances in which urticaria is the clinical manifestation of specific food sensitivity.

From the standpoint of practical demonstration, elimination diets, as advocated by Rowe¹ and others,^{2,3} hold a deservedly high place in the management of the food-sensitive patient; such a method of investigation requires time, patience and accuracy of judgment on the part of the clinician but frequently focuses direct attention upon the offending substances. X-ray studies in this field began in 1915 when Crispin⁴ first observed the appearance of angioneurotic edema of the pylorus roentgenologically. Two years later Christian⁵ reported two

instances of probable digestive tract allergy in which abdominal pain and radiologic findings had led to laparotomy for gross organic disease. In 1921 Duke⁶ first described roentgenographic appearances of the stomach in a specific food sensitivity, and subsequently Eyermann,⁷ Rowe,⁸ Andresen,⁹ Fries and his associates^{10,11} and others have contributed to the study of such changes in all segments of the alimentary tube. This method has been brought to such a stage of development that, in the opinion of the author, it may serve as a point of reference to which the results of other types of investigation may be directed for confirmation; when, for example, elimination diets have apparently singled out a specific food sensitivity, the diagnosis may be substantiated by the performance of a gastrointestinal x-ray series, using first the usual barium suspension as a control, to be followed by the incorporation of a sample of the suspected food allergen with the barium mixture. Such studies have not gone unchallenged; Pendergrass and his associates,¹² Ravdin,¹³ Fantus,¹⁴ Macy¹⁵ and others have demonstrated changes in the small bowel pattern and motility on the addition of various substances, including 50 per cent glucose solution, egg white, olive oil, milk, bran and other nutritive elements, to barium suspensions. However, these alterations do not appear to be of the same order of divergence from the normal as do those marked changes observed in the individual who presents evidence of true food sensitivity and who usually exhibits the subjective and/or objective manifestations of his sensitivity during the performance of the study although he may be unaware of

* From The Jewish Hospital, Philadelphia, Pa.

administration of the allergen. In their study of gastrointestinal allergy in children in 1943, Fries and Mogil described radiologic changes which they concluded were "effects due to allergenicity of food and not to its nutritive content" inasmuch as subjects who had lost their sensitivity to specific foods presented normal roentgenograms when retested with the same barium food mixtures. In 1941 Thomas and Renshaw¹⁶ brought attention to the method of direct proctoscopic observation of the reaction produced by contact of an allergen with the rectal mucosa and found erythema, edema, vascular engorgement and hemorrhage in varying degrees. Similar mucosal effects in the stomach have been reported by gastroscopic observation after oral administration of suspected allergenic substances. The considerable literature regarding leukopenic and eosinophilic phenomena has represented another aspect of the search for knowledge concerning digestive allergy; the original observations by Rinkel¹⁷ and Vaughan¹⁸ have recently undergone revision and elaboration by Randolph¹⁹ which further enhances the value of studies in the investigation of individual patients.

To these methods it is now proposed to add a new type of investigation. This is the employment of a balloon-tipped, double lumen intestinal tube by means of which numerous phenomena may be studied from kymographic recordings. By this method it is possible to observe the degree of tonus and the rate of motility in a selected segment of the intestine and the changes in these functions occasioned by the oral or tubal introduction of suspected food allergens. The reaction interval and duration may be determined and the effect of therapeutic agents may be evaluated *in vivo*.

METHOD

The device employed in this study is illustrated in Figure 1. It consists of a Miller-Abbott tube, the suction lumen of which is clamped off except for the removal of intestinal secretions or the introduction of selected foods, indifferent control agents

or pharmacologic products. The other lumen, capped at its distal terminus by the balloon, is connected proximally to a closed, diaphragm-capped chamber in such a manner that pressure changes in the chamber may be communicated to an

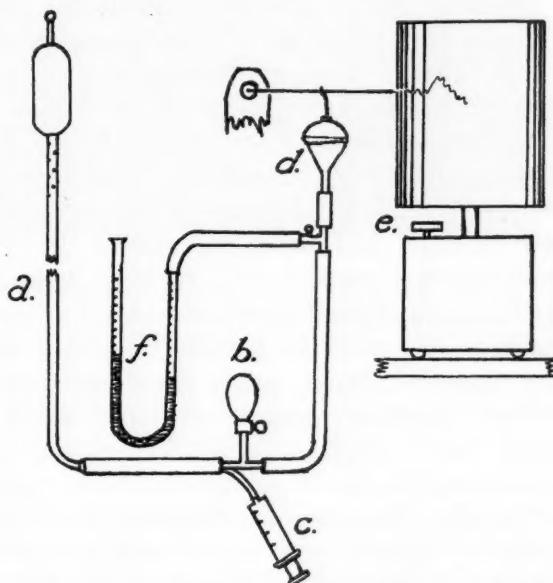


FIG. 1. Apparatus for procedure: (a) Miller-Abbott tube; (b) bulb for inflation of balloon-diaphragm system; (c) syringe for instillation of test substances; (d) pressure chamber-diaphragm unit; (e) electrically driven, timed kymograph; (f) water manometer.

accurately timed electrically-driven kymograph; a T-tube inserted into this system is attached to a water manometer in order to record pressure changes in cc. of water, and to correlate these measurable changes with alterations of amplitude on the kymographic recording. In order to obtain some measure of uniformity in the present study all observations have been made after implantation of the balloon in the jejunum, approximately opposite the ligament of Treitz, as observed fluoroscopically. Routinely after passage of the tube into the duodenum sufficient air was introduced into the balloon to record a manometric pressure of 10 cc. of water. This was done both to facilitate passage of the tube into the jejunum and to provide an easily compressible surface against which the wall and contents of the intestine might exert pressure. Once the balloon was found to be situated in the desired segment, kymographic recordings

were made during the "resting" phase of small intestinal activity and after the introduction, singly, at intervals of not less than twenty minutes, of various control and suspected food substances in liquid or suspended form.

In 1939 Wangensteen,²⁰ measuring the intraluminal pressure of isolated loops of small intestine during the course of a surgical operation for intestinal obstruction, reported pressures of 4 to 14 cc. of water. One year later Brody and his co-workers²¹ clearly described the characteristic rhythmic contractions and tonus alterations of the stomach and small bowel. In 1943 Abbott and his associates²² made a study of intraluminal pressures in various segments of the digestive canal, using their well contrived "pressure capsule" to detect alterations which might then be transmitted to an automatic recording system. As a result of parallel observations employing both the pressure capsule and the balloon technics Abbott pointed out the superiority of the pressure capsule method, stating that "the balloon record, which in a rough way is a measure of the capacity of the gut lumen over a limited area, shows a pattern of far greater variability, indicating that not every contraction or relaxation of the intestinal musculature brings about an appreciable change in intraluminal pressure." However, as a matter of availability and cost of apparatus, the balloon method was chosen for the study on which this report is based, and the basic and phasic changes in pressure in normal individuals have been found to parallel closely those observed by Abbott's group.

RESULTS

In normal individuals tracings by means of this procedure have exhibited the rhythmic contractions and tonus alterations which have been reported by previous workers. A typical normal kymographic recording is illustrated in Figure 2. Due to the initial introduction of sufficient air to produce a manometric pressure of 10 cc. of water, measurement of the basal pressure

cannot be performed accurately in all cases inasmuch as some diastolic pressure readings must lie below that level. The phasic pressure changes in twenty normal patients have been found to reach a maximum of 12 to 38 cc. of water spontaneously or after the intraluminal instillation of water, 10 per cent glucose solution or liquid foods to which no specific sensitivity has been known or suspected. These foods have included beef extract, wheat extract, tomato juice, fruit juices, milk, etc. In these normal individuals the rhythmic pressure changes occasioned by introduction of such substances rise above that recorded in a basal period but do not rise beyond those found spontaneously in other normal subjects nor in the same subjects at other times. The frequency of the phasic waves is usually increased immediately after introduction of such substances, but after periods of forty seconds to three minutes this heightened effect subsides and the fasting rhythm is resumed. This probably represents the time interval necessary for the local bowel segment to accustom itself to the distending effect of the 10 cc. quantities of fluid introduced or may represent the time necessary to propel the liquid beyond the space occupied by the balloon. While it is readily admitted that this method of observation cannot be used for the precise measurement of intraluminal pressures, relative constancy of the phasic pressure changes so observed does permit its use as a control agent against which more violent reactions might be contrasted if found to occur.

In cases of intestinal food allergy the tracings secured prior to introduction of allergenic foods have shown no divergence from the range of variability found in non-allergic individuals. The frequency of contractions, rhythmicity, duration and amplitude of phasic pressure waves have been quite comparable throughout. In this group, after the position of the tube has been verified fluoroscopically and the initial pattern has been inscribed, a series of indifferent or non-suspect elements is introduced through the tube routinely; these

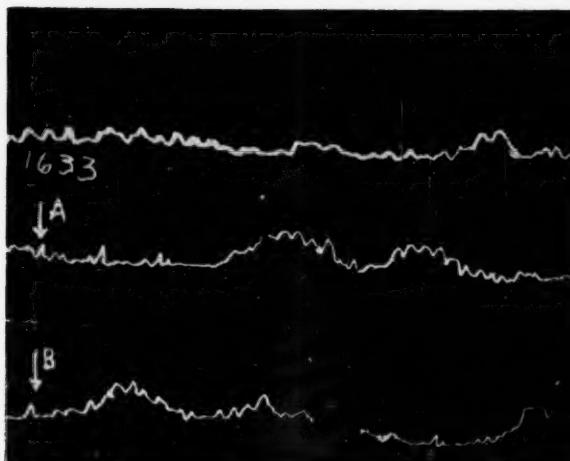


FIG. 2

FIG. 2. Normal tracing. Upper line demonstrates continuous fluctuations in intraluminal pressure; at point A 10 cc. of 10 per cent glucose was introduced and stimulated phasic pressure waves in forty-five seconds; twenty minutes later an almost identical pattern of phasic pressure waves was recorded spontaneously in line B. Manometric pressure in each line did not exceed 28 cc. of water.

FIG. 3. Case 1, milk allergy. Tracing illustrates abnormal intraluminal pressure changes following instillation of 10 cc. of milk, the initial severe contraction occurring in two minutes, with a return to the "resting" level in four minutes. Peak manometric reading was 78 cc. water.

have included 10 to 30 cc. portions of 10 per cent glucose solution, olive oil, milk, powdered egg suspensions, beef extract and water-thinned purees of a variety of common foodstuffs. Just as in the non-allergic subjects the instillation of simple nutritive elements in small quantities produces transient changes of amplitude and frequency of the phasic pressure waves, which still fall within the limits noted spontaneously in normal subjects or in the same individuals at other times without the introduction of anything by tube. This control period is followed by the instillation of 10 cc. quantities of foodstuffs which, by reason of history, elimination diets or prior x-ray study, are suspect. The nature of each test substance is, of course, concealed from the patient throughout the period of observation in all cases.

Following the instillation of foods allergenic to a given individual, the alterations in the kymographic tracings have been notable. Furthermore, these alterations, usually violent, have frequently been accompanied by the subjective manifestations of which the patient had previously complained. The interval between the contact of the allergenic food with the

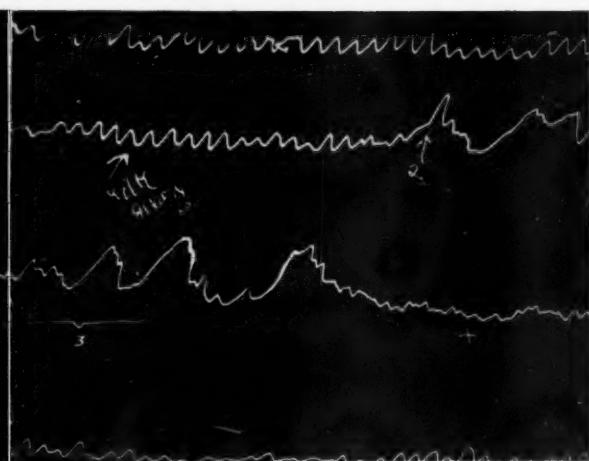


FIG. 3

jejunal mucosa and the onset of abnormal kymographic phenomena has varied from two to twelve minutes in this series, with a mean of four minutes. The onset of the reaction phase is marked by a rather gradual increase in the height and duration of the phasic pressure waves. At times, as illustrated in Figure 8, the individual waves increase rapidly in acuity and amplitude and the interval between successive contractions decreases progressively until a maximum point of activity, after which there is a gradual recession in reverse sequence. In other cases there is superimposed upon more moderately accentuated phasic pressure waves a series of acute spiking inscriptions of varying amplitude, all marked by their extreme height as compared with any change in the underlying basic rhythm; Figure 3 represents an example of this type. The total duration of the reaction to a given allergen varies from two to eighteen minutes with, in this series, one instance in which the violence of the reaction culminated in regurgitation of the entire tube. There does not appear to be any constant relation between the duration of the reactive phase and the severity of the contractions as measured either in fre-

quency or in amplitude. In the present series of twenty-two cases a wide variety of combinations has been secured. In all cases, regardless of the type of configuration recorded, the manometric pressures have well exceeded the highest readings found in non-allergic reactions. These have varied from 56 cc. of water, well above normal readings, up to 152 cc. of water, a reading obtained during a particularly violent subjective reaction of intense cramping pain. The range of manometric pressures observed in the allergic patients is thus seen to be sufficiently removed from the 12 to 38 cc. readings during control tests to be significant. This factor, combined with the coincident appearance of altered kymographic patterns of localized intraluminal pressure changes, seems to enhance the specificity of the study. Once the reactive phase characteristic of that particular jejunal segment has subsided, the kymographic pattern returns to its pretest level although the patient may continue to evidence further symptomatology as more distal areas are successively involved for variable periods of time; in other instances the subjective manifestations subside with return of the tracing to resting levels, as though the reactive mechanism had been exhausted or the allergenic substance itself had been, in a manner of speaking, neutralized. In a few instances a second instillation of the known allergen has been performed after various intervals of time during the course of the same intubation, but this group of observations is as yet too small to permit deductions or conclusions. In a single instance, Case 1, the tracing was marked by a rhythmic pattern due to respiratory movement; this isolated case presented unusual postoperative tension of the abdominal wall.

The data and tracings from two of the confirmed cases of gastrointestinal food allergy studied by this method to date will serve to illustrate the foregoing observations. Their presentation is detailed for the dual purpose of describing the mode of application of the procedure and of emphasizing

the confused and obscure clinical patterns which characterize so many instances of gastrointestinal food allergy.

CASE REPORTS

CASE 1. M. A., a female aged forty-seven years, presented a lengthy history of digestive disturbances beginning with abdominal cramps and constipation in childhood, requiring constant medical attention. In 1941 she developed epigastric fullness and distress about one hour after meals; after a few months symptoms abated, recurring thereafter irregularly. In 1945 the symptoms became severe and in early 1946 her first gastrointestinal x-ray series disclosed an ulcer on the lesser curvature of the stomach. On a modified Sippy regimen her response was unsatisfactory and in the fall of 1946 the position and nature of the lesion was confirmed gastroscopically. However, when treatment was intensified, anorexia, nausea and vomiting occurred although there was no evidence of any obstructive phenomena. On December 2, 1946, total gastrectomy with esophagealjejunal anastomosis was performed. Examination of the resected tissues disclosed "chronic ulcer of the stomach; chronic lymphadenitis"; no evidence of malignancy was found. The ulcer was 2 cm. in diameter, mid-way between the cardia and pylorus on the lesser curvature, was firm and indurated and extended to within 2 mm. of the serosa. Convalescence was stormy. Appetite failed to return and various modifications of the ulcer diet failed to alleviate the high abdominal pain, nausea and vomiting; weight, formerly about 120 pounds, had dropped to 106 pounds preoperatively and 88 pounds on hospital discharge. Despite supplementary proteolysates, frequent feedings according to the Sippy regimen, crude liver extract and various forms of therapy, the weight was still at the level when the patient was first seen on April 25, 1947. Watery, explosive stools had occurred after most feedings, three to six times daily since the time of operation, but none had contained gross blood and none had been tarry.

The patient appeared ill and emaciated. The abdomen was scaphoid and extremely thin-walled; peristaltic movements were readily observable as rapid and forceful and, at times, were accompanied by visible expressions of pain. There was questionable high epigastric tenderness. Blood count showed a borderline anemia;

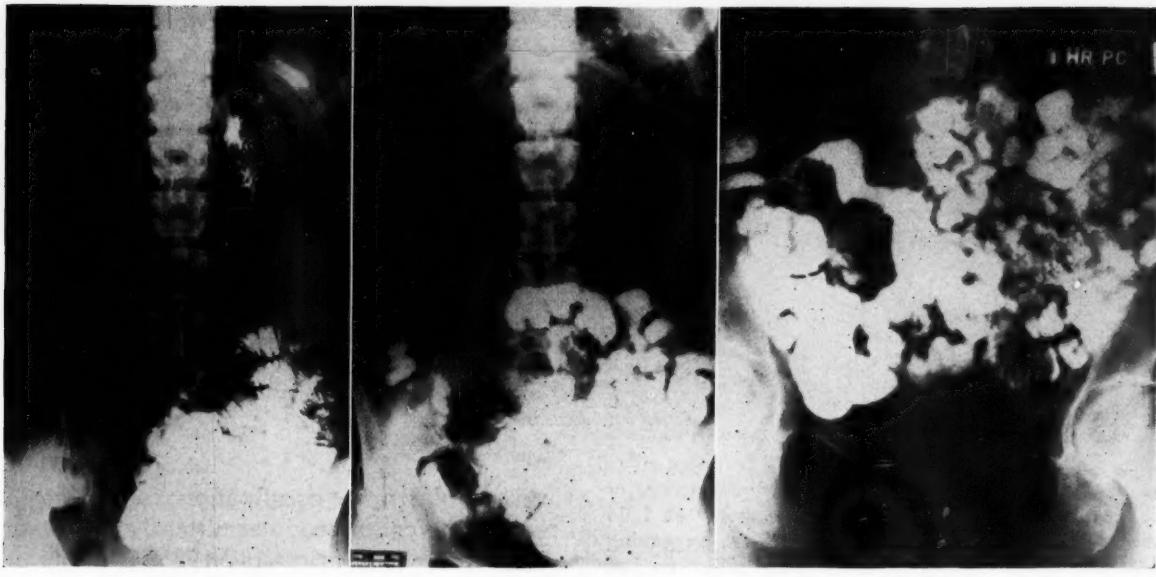


FIG. 4. A, x-ray four and one-half hours after plain barium meal; motility was delayed but the pattern was normal; B, three-quarters of an hour after introduction of milk the pattern was distorted by segmentation, pooling and narrowing or dilatation of the loops; C, one hour after milk there were similar but more advanced alterations.

sedimentation rate was normal; stool examinations were negative for occult blood and were abnormal only in containing some undigested starch granules.

Partly because of the poor physical condition of the patient and partly because the possibility of food allergy had been obscured by the organic nature of the pre-existing disorder, intubation study was not made until September 26, 1947. Figure 3 represents the tracing made on that date. The tube was readily introduced orally, passed through the jejunal stoma and on to a position opposite the ligament of Treitz. A control instillation of 30 cc. of 10 per cent glucose solution failed to alter the tone or to make any alteration of the strong intercurrent respiratory rhythm which was caused by the contracted abdominal wall. However, two minutes after instillation of 10 cc. of milk, marked irregular contractions appeared, produced sharply abnormal phasic pressure changes and were reflected in the patient's complaint of cramps and nausea. The duration of the reaction was two minutes, after which the inscription resumed its former pattern; however, the patient's crampy pain persisted and was relieved only after passage of a watery stool about twenty minutes later. On October 2, 1947, roentgenologic studies,* illustrated in Figure 4,

were reported as follows: "Initially the jejunum and proximal ileum fill very rapidly and present an entirely normal pattern. Between 15 minutes and three hours, however, there is very little further progress of the meal. Fluoroscopy was done in three hours but no film was taken. Even at four and a half hours the meal has not reached the cecum but the pattern still remains normal. After the four and a half hour film, the patient was given a glass of milk and films were taken in three quarters of an hour and one hour. These show very definite change in the appearance of the small bowel. Motility is increased so that the barium mixture passes into the cecum. The normal pattern is disturbed and there is segmentation, pooling and areas of narrowing and dilatation. In the terminal ileum the lumen is so reduced that it suggests the string sign seen in regional enteritis. This does not appear to be constant and is probably due to spasm rather than organic change."

Since studies had thus clearly demonstrated an intestinal milk allergy, a new phase of therapy was instituted. At first desensitization with milk propeptans was attempted according to the method described by Urbach²³ and while the patient was partially relieved, some abdominal burning and distress continued to appear about fifteen minutes after feedings, lasted for one hour and then disappeared until the next feeding. After two weeks a second intubation study was performed, the tracing of which is repre-

* Roentgenologic studies embodied in this report were performed by Harold J. Isard, M.D. and William Serber, M.D., Philadelphia, Pa.

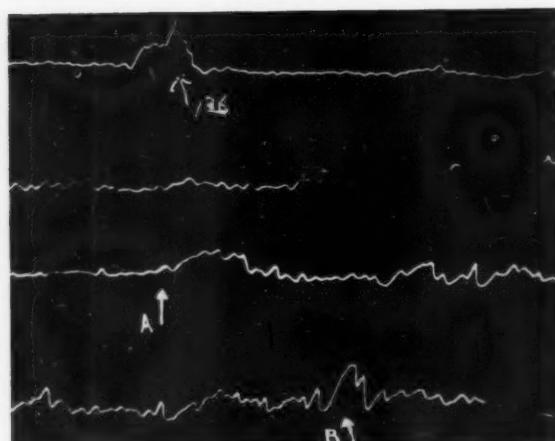


FIG. 5. Following treatment with milk propeptan, of which two capsules were given forty-five minutes prior to instillation of 10 cc. of milk. The arrow at 1:26 marks artefact produced by sneezing. A, beginning reaction occurring six minutes after milk; B, last abnormal pressure change seven minutes later.

sented in Figure 5. Forty-five minutes after swallowing two capsules of milk propeptan, 10 cc. of milk was instilled. Six minutes later the patient complained of discomfort and almost immediately thereafter the basic tonus level rose and phasic pressure waves showed marked accentuation for a period of seven minutes, culminating in a sharply severe crampy pain at the height of one spastic phase. Thereafter the tracing reverted to its former status.

A few days later, after abstinence from milk and milk products, the administration of thephorin (phenindamine, Roche) 25 mg. twice daily was begun, and milk was permitted in small amounts throughout the day, increasing to a total of 1 pint daily. During the six months since this change in therapy, diarrhea and abdominal cramps have occurred in widely separated isolated episodes. Gradual improvement in weight and nutrition have occurred. The dosage of thephorin has been established at 25 mg. once daily although the daily intake of milk is divided into several small feedings. A tracing taken on December 16, 1947, is recorded in Figure 6; after the instillation of 50 cc. of milk it shows no significant aberration from the resting pattern for this patient.

CASE II. H. L., a male aged forty-four years, had recurrent attacks of right lower quadrant pain beginning in 1915, at the age of twelve years. Two years later appendectomy was performed and he was free of digestive symptoms until 1921 when he developed pain in the right upper quadrant, with radiation to the right

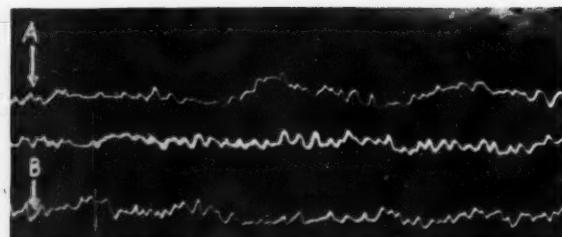


FIG. 6. Tracing made after treatment with phenindamine. A, introduction of 10 cc. of 10 per cent glucose solution followed by phasic pressure waves, the peak reaching a manometric reading of 22 cc. of water. B, instillation of 50 cc. of milk followed by no significant alteration from the resting phase in the middle inscription.

subscapular area, constipation and heartburn. Symptoms continued intermittently and in varying degrees of severity until 1925, at which time a clinical diagnosis of duodenal ulcer was made and x-rays were reported as "suggestive of atypical ulcer." An ulcer diet was poorly tolerated and the syndrome remained active. During the next five years gastro-enterologic and radiologic opinions leaned toward peptic ulcer plus gallbladder disease but appropriate therapeutics did not effect consistent improvement. In 1930 the patient discovered his own untoward reaction to certain foods, notably milk, malt products, lima beans, peas and chocolate, and in 1935 x-ray disclosed a normal upper digestive canal and gallbladder but generalized colonic spasticity. During the following nine years there were three attacks of "food poisoning," consisting of nausea, vomiting and diarrhea of twenty-four hours' duration; following the acute phase of the last such attack, there was anorexia and simple diarrhea for about six months. At that time the stools were found to contain ova of *Endamoeba histolytica* and appropriate therapy effected a cure. However, stools continued to be soft, and in 1941 another gastro-enterologist first suggested the possibility that an allergic state might have been responsible for the original symptom complex or might represent an acquired sensitivity. In 1945, about three hours after a meal which included clams, the patient suffered vise-like high epigastric pain of sudden onset, became pale, sweaty and weak; the pulse rate was accelerated and the upper abdomen became rigid. An acute coronary episode was suspected but after seven hours the pain had shifted to the right upper quadrant, with right subscapular radiation. Ensuing studies, including electrocardiogram, cholecystography and

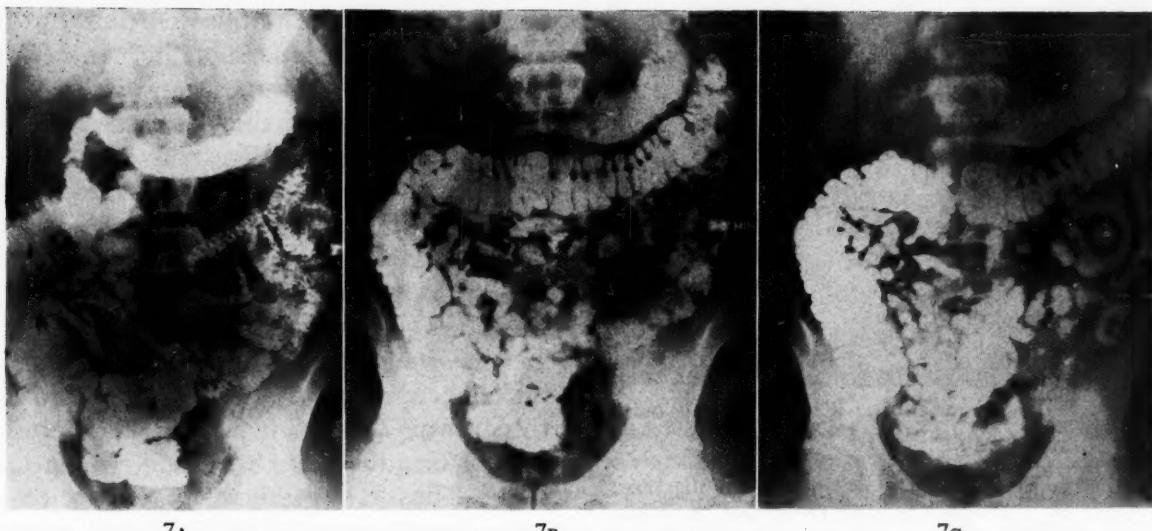


FIG. 7. Case II, A, x-ray seventy-five minutes after administration of plain barium meal; there was a normal small intestinal pattern with a continuous stream of barium from the stomach to the terminal ileum; B, thirty minutes after ingestion of clams: there were segmentation of the loops, a suggestion of coarsened mucosal folds, hypertonicity and irregularity of the caliber; the head of the column at the splenic flexure; C, thirty minutes later there was no progress or change.

sigmoidoscopy, were negative. A bland diet was instituted, but diarrhea continued intermittently.

When this patient was first seen in August, 1947, physical examination revealed nothing of significance. Blood count, sedimentation rate and stool examinations were entirely normal. Biliary drainage resulted in the delivery of a well concentrated specimen which was normal on microscopic examination. Sigmoidoscopy and examination of direct smears from the sigmoid and rectum were negative. Stool cultures disclosed only predominant coliform organisms. Electrocardiography and cardiac consultation indicated no evidence of cardiovascular disease.

On October 9, 1947, roentgenologic studies were reported as demonstrating normal esophagus, stomach and duodenum and normal colon except for some irritability and spasticity of the cecum and proximal ascending colon; the mucosal pattern appeared entirely normal. With regard to the jejunum and ileum, the radiologists reported: "The calibre of the jejunal loops is normal throughout and the mucosal pattern is of the normal feathery type. Progression through the small bowel is quite rapid and at the end of 30 minutes the head of the meal has reached the terminal ileum. The film at this time discloses a continuous stream of barium from the stomach to the terminal ileum. Despite the rapid transit through the small bowel, there does not appear to be too rapid emptying of the stomach. The coils of the ileum appear normal

and there is no undue hypertonicity or segmentation. Seventy-five minutes after administration of the barium meal there is again no evidence of segmentation or undue hypertonicity. At this time the patient was given six clams. A film exposed thirty minutes later discloses a marked change in the appearance of the small bowel pattern. There is hypertonicity of many of the loops, the lumens of which are irregular in calibre; segmentation is apparent and there is a suggestion of some coarsening of mucosal folds. The head of the barium meal has progressed to the splenic flexure. The next film was exposed 60 minutes after the meal and the appearance remains quite comparable to that noted on the 30-minute film." Figure 7 demonstrates the significant plates in this case.

It was not until January, 1948 that an opportunity arose for intubation study, a kymographic recording of which is represented in Figure 8. After negative trial instillations of 10 cc. quantities of milk and of lamb extractives, 10 cc. of fresh clam juice was passed into the jejunum. Two minutes later an initial severe contraction was recorded coincidentally with the patient's complaint of high epigastric pain. This was followed in eighty seconds by a stronger wave of hypertonus and thereafter by a succession of strong contractions which progressively increased in frequency, acuity and amplitude as recorded on the kymograph; this soon mounted to a six-second interval between subjectively



FIG. 8. Sections from tracing illustrate a progressive increase in acuity, amplitude and frequency of exaggerated pressure changes in response to allergenic food. Clam juice, 10 cc., was instilled at the point marked by the upper arrow. There was an initial severe contraction in two minutes, followed by rapid progression culminating in regurgitation of the tube in six minutes.

painful contractions which eventuated in violent retching and regurgitation of the tube.

Since the date of this study, elimination of clams and other offending foods from the patient's dietary has resulted in marked amelioration of digestive tract symptoms.

COMMENTS

The difficulties attending the diagnosis of gastrointestinal food allergy are notorious; they have received comment from Duke,²⁴ Moore²⁵ and almost every other investigator in this field. It has been stated repeatedly that food allergy can mimic, in part or in whole, almost any gastrointestinal disease; the manifestations depend upon the segment of the alimentary tract in which the reaction occurs and upon the qualitative nature and quantitative extent of the reaction. Any portion of the digestive tube may be the site of an allergic reaction. Thus Fries and his co-workers found x-ray evidence of gastric reactions in children in whom subjective symptoms appeared promptly after ingestion of allergenic foods; Hampton and Cooke²⁶ reported abnormal segmentation of the small intestine in cases of delayed type of food allergic reaction; many x-ray studies have disclosed colonic abnormalities following oral administration of food allergens, and the proctoscopic observations of Thomas

and Renshaw have implicated directly the mucosa of that segment of the canal. The present intubation studies not only confirm the susceptibility of the jejunum but also suggest that gastric digestion fails to denature the foods thus far used in this study in such a manner as to destroy their allergenicity. At this point it will be recalled that in Case II, clams appeared to elicit similar small bowel responses when given by mouth in the roentgenologic study and when introduced directly into the jejunum by tubal instillation. This has been demonstrated in other cases with egg, wheat and milk. Thus it would seem that without regard to the precise chemical or hormonal reaction which mediates the local response, there are food-specific allergens which are capable of initiating certain phenomena within two minutes of the time they come into contact with the jejunal mucosa and which are not sufficiently altered by gastric digestion to prevent these effects. The question of whether the minimum interval of two minutes represents the period necessary for local tissue reaction, absorption, hormonal elaboration, neural intervention or any combination of these modalities remains unanswered at this time.

In this study, after passage of the tube into the duodenum, sufficient air was introduced routinely into the balloon to record a manometric pressure of 10 cc. of water. It is readily seen that this would preclude the possibility of accurate measurement of basic intraluminal pressure. Yet, as previously mentioned, phasic pressure changes of 12 to 38 cc. of water were obtained during "resting" periods and following the introduction of non-allergenic liquid foodstuffs. In view of the presence of the balloon-air mass these phasic pressures would seem to represent (1) the rhythmic contractions characteristic of the constant activity of the small intestine, (2) the force of intestinal muscular contraction elicited as a simple response to the distending effect of the balloon, (3) the force produced by peristaltic waves attempting forward propulsion of the balloon itself or of liquid past the

partial obstruction produced by the balloon or (4) at times, a summation of those factors.

The studies of Posey and his group,²⁷ using a balloon technic in ileostomized humans, have clearly demonstrated three configurations of small intestinal activity, of which one is a constant series of rapid, rhythmic contractions, another of larger, slower contractions which are sometimes propulsive and a third which is produced by tonus waves on which the other types are superimposed; when propulsion occurs in the third type, it is invariably associated with superimposition of the second type of wave. Attempts at propulsion are thus seen to be characterized by considerable augmentation of intraluminal pressure. This is still, however, within observed normal limits. In the experiments by Abbott in which water was injected proximal to a distended balloon in sufficient amount to simulate the intraluminal distention occurring in acute artificial intestinal obstruction the phasic pressures rose only as high as 50 cc. of water.

On the other hand, after the introduction of an allergenic food the components making up the total reaction must include those normally present plus elements peculiar to the intestinal allergic reaction. Those elements, according to roentgenologic, gastroscopic and pathologic evidence, consist of local mucosal edema and increased muscle tonus, at times exaggerated to high degrees of swelling and spasticity. It is probable that both these elements play a role in production of the kymographic records in this study. Local edema may well serve further to occlude the jejunal lumen at and proximal to the site of the balloon, at least to a degree at which both regular phasic and interjected stronger muscle contractions are more sharply communicated to the kymographic tracings. The studies made by Wing and Smith²⁸ on sensitized guinea pigs showed no alteration in small bowel pattern even when the animals were in fatal anaphylactic shock; in these experiments it seems probable that the intestinal wall did not assume the function of shock organ.

However, in commenting on that presentation, Gray referred to the studies by Gray, Harten and Waltzer^{29,30} of the gross and histologic allergic reactions in rhesus monkeys and concluded that the spastic phenomena were secondary to the tremendous edema of the mucous membrane at the site of the reaction. While it is likely that local edema is an early and marked intestinal mucosal reaction to the presence of an allergen, and possible that spastic phenomena are secondary thereto, the wave and spike nature of the inscriptions in the kymographic recordings here obtained seem to represent too dynamic an activity to be the result of edema alone. Rather, they embody characteristics which appear attributable largely to gross exaggeration of normally present phasic changes and to the interjection of strong spastic contractions. The elevation of the entire tracing during an observed period of reaction, slightly above the baseline noted before and after the reactive span, may represent a prolonged increase in basic tonus or the constrictive effect of mucosal edema upon the balloon or, again, a combination of those factors.

On the basis of the results in this study the intubation procedure appears to afford a means of securing confirmation of the specificity of food allergens in a given individual. It may be performed in such a manner as to test a number of foodstuffs during the course of a single intubation, instilling them singly at intervals of twenty minutes since, in our experience, the longest period of reaction latency has been eighteen minutes. Thus far the feasibility of instilling additional trial foods after the subsidence of a typical reaction to an allergenic one has not been determined; this procedure and that of repeating instillation of the same allergenic food after varying intervals of quiescence may afford further insight into the mechanism of food allergy generally. The specificity of the method seems to be equal, if not superior, to that of the radiologic method utilizing food-barium mixtures; however, the radiologic study is

limited to the trial of one or, at most, two foodstuffs during a single period of study, and extension of the procedure to a larger series of suspected foods promotes the risk of overexposure to radiation.

CONCLUSIONS

The intubation procedure is not recommended as a routine method for the discovery of food allergy. At the present time this disorder is most apt to be suspected by carefully detailed case histories. Routine gastrointestinal studies and x-rays then serve to exclude observable organic lesions. Clinical observation, elimination diets and the study of leukocytic phenomena are useful as a screening process for the implication of specific foodstuffs. Finally, roentgenologic study with barium mixed with suspected foods and/or use of the intubation procedure may then be employed to substantiate the diagnosis. This appears to be the optimum point for application of the intubation study in the diagnosis of the individual patient and, as previously indicated, this procedure has certain advantages over the roentgenologic method. In a more general sense, the method as here described, or in greater elaboration, provides an additional method for the investigation of intestinal food allergic phenomena. From a study of the kymographic records thus far obtained there appears to be evidence for the presence of exaggerated phasic motor changes and the interpolation of spastic contractions of the intestinal muscle, both being superimposed upon an elevated intraluminal pressure. This latter may be secondary to local reactive edema, or to reactive increase in tonus or to a summation of these factors.

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I. Motility of the Human Esophagus in Control Subjects and in Patients with Esophageal Disorders*

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WHEN the human esophagus is studied fluoroscopically after administration of a barium meal, this organ manifests tone (as indicated roughly by the luminal caliber) and phasic activity that comprises three types of waves: primary, secondary and tertiary.¹ The tone and contractions of the human esophagus have, however, been recorded infrequently by the balloon-kymograph technic, and such studies as have been made pertain to strictly physiologic problems.²⁻⁵ Since balloon-kymograph records of esophageal motility in various clinical conditions were not available, we have used this method in fourteen control subjects without esophageal disorders, in four patients with cardiospasm, in four with scleroderma and in two with mechanical obstruction of the esophagus.

The technic used was that described by Ingelfinger and Abbott,⁶ with the minor modification that the Miller-Abbott tube connecting the esophageal balloon to the recording device was only 100 cm. long. In this system a relatively constant pressure (20 to 25 cm. of water) forces air into the balloon until the resistance of the esophageal wall permits no further inflow. The volume of the balloon therefore indicates the resistance of the esophagus to a distending force and may be considered an expression of esophageal tone. When the volume fluctuates because of phasic activity, tone is calculated as the mean volume of air contained in the balloon between the extremes of phasic contraction and relaxation.

Records were obtained by two procedures: The balloon was allowed either to progress down the esophagus with peristaltic activity or was maintained in one of three standard positions by fastening the tube at the nose. The standard positions, which were invariably ascertained by fluoroscopic means, comprised: (1) upper esophagus—balloon situated behind the manubrium sterni and extending upward into the suprasternal notch; (2) mid-esophagus—balloon at the pulmonary hila; (3) lower esophagus—distal end of the balloon just above the diaphragm. The motility recorded under these conditions is initiated by the presence of the balloon. Except as indicated, the subjects were asked not to swallow. Frequently, however, a subject might swallow involuntarily because of the irritation caused by the presence of the balloon in the esophagus or by the tugging of the tube in the nasopharynx. It is apparent that our records, obtained by stimulating the esophagus with a large, pliable but non-fluid bolus, can be compared only in general terms with motility studies obtained by other means.

CONTROL SUBJECTS

When the balloon was inflated in the upper esophagus and allowed to progress with peristaltic activity, an average of 87 seconds was required before the balloon entered the stomach. Repeated determination of the esophageal transit time in the

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same subject yielded results that were consistent in some but not in all individuals. The variation in transit times in different subjects was considerable, extending from fifteen seconds to five minutes and forty-five seconds. The significance of these transit

stomach may at any moment be recording simultaneously from more than one area of the esophagus and may occupy, as it passes through the cardia, a partially intragastric position. For these reasons we believe that the position of the balloon should be

TABLE I
ESOPHAGEAL MOTILITY IN CONTROL SUBJECTS

Subject	Diagnosis	Tone (cc. of air in balloon)			Height of Wave (cc. of air expelled from balloon)			Frequency (No. of waves per minute)		
		Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower
A. S.	Constipation	6	8	7	4-12	14	8-9	9	6	10
O. F.	Functional gastrointestinal disorder	17	12	11	0	7-11	6-8	0	6	6
A. S.	Hypertension	17	11	11	3	4-9	3-9	15	11	12
J. C.	Functional gastrointestinal disorder	10	10	5	4-6	15	3-8	11	6	12
A. M.	No disease	15	12	12	3	21	12	12	4½	6½
F. J. I.	No disease	18	23	24	7-10	17-29	13-19	7	6	6½
F. J. I.	No disease	23	22	6
P. K.	No disease	7	9	7	3-5	9	6	16	6	8
S. L.	Functional gastrointestinal disorder	11	14	11	4-6	19	11	9	5	7
A. S.	Functional gastrointestinal disorder	10	12	4	9-14	7	7
M. M.	Functional gastrointestinal disorder	8	7	7	2-10	12-14	10	7	6	11
W. H.	Cholelithiasis	8	6	6	3	12	10	9	6	6
J. L.	Gastric ulcer	10	14	15	5-8	9-11	10	9	6	6½
N. B.	No disease	9	8	8	3	8-10	10-13	10	8	8
F. S.	Diabetes	10	16	16	13	6	7
Range	7-18	6-23	5-24	2-12	4-29	3-19	0-16	4½-11	6-12
Average	11.3	11.8	10.9	4.5	13.5	9.8	9.5	.65	8.1

times is limited for the esophagus has to propel not only a balloon but an attached tube (weight = 40 Gm.) which encounters variable friction in passing through the nares.

Motility records obtained as the balloon passed down the esophagus were generally unsatisfactory, partly because of the variations in transit time, partly because the exact position of a moving large balloon was difficult to determine. A condom balloon, which measures 5 cm. in length when inflated outside the body, is moulded by the esophagus into a cylinder of smaller diameter but greater length. Because of this length, a balloon travelling toward the

fixed if satisfactory motility records are to be obtained from the human esophagus by our method. On the other hand, Hwang et al.,⁷ who used a quite similar method in dogs, found the motility record obtained as the balloon moved down the esophagus so characteristic that small changes in the wave pattern were considered to be of major significance.

Records obtained by maintaining the balloon in the three standard positions yielded motility patterns that were quite characteristic for each position. In the upper position the wave pattern was irregular and characterized by excursions of small amplitude. By way of contrast, large and

well defined waves succeeded each other in regular sequence when the balloon was inflated and maintained in the mid-position. In the lower position, just above the cardia, contractile activity was less pronounced and usually less regular than that character-

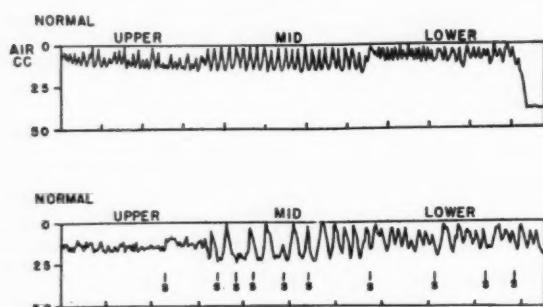


FIG. 1. Records of esophageal motility in two normal subjects. In the lower record the motility pattern is affected by repeated swallowing, indicated by "S."

istic of the mid-position. Details concerning tone and phasic activity are given in Table I. Figure 1 shows representative records obtained in the three standard positions.

The large waves manifest in the mid- and lower esophagus were decidedly peristaltic in nature. Coincident with their appearance a strong tug was felt at the nasal end of the tube, and fluoroscopic observations showed contraction rings sweeping down over the esophageal balloon. These waves consequently are probably identical with the secondary peristaltic waves described by Meltzer.⁸ The absence of large excursions in records obtained from the upper esophagus is also consistent with Meltzer's observation that secondary waves do not arise in the cervical portion of this organ. Secondary peristaltic waves arising in the mid-esophagus may also be observed by the fluoroscopist when this area is distended by fluid contents that either regurgitate from the lower esophagus or remain after a primary wave has passed.

Swallowing, whether voluntary or involuntary, changed but did not abolish the local motility stimulated by the presence of the balloon. (Fig. 1.) In the upper esophagus a large wave frequently was superimposed on the irregular spontaneous motility. In the mid- and lower esophagus

the changes produced depended to some extent on the phase of the spontaneous motility. Swallowing during the phase of relaxation tended to increase the degree of relaxation and delayed the onset of the next wave but this wave thereupon generally was augmented both in height and duration. Swallowing during the phase of contraction yielded less constant results—the wave in progress was sometimes augmented, sometimes inhibited; occasionally the size of the subsequent wave was increased. These observations, on the whole, are in harmony with the concept that a wave of relaxation precedes a wave of contraction.

Carlson and Luckhardt,³ in studying the motility of the human esophagus with a balloon method, recorded small tonic contractions occurring regularly at less than two-second intervals, larger but irregular tonic contractions and occasional peristaltic waves. Since the balloon used in these studies was quite large (condom, 3 to 4 cm. in length), the dissimilarity between our records and those of Carlson and Luckhardt is surprising. The pressures used by these investigators to inflate their balloon was, however, only 3 to 6 cm. of water, about one-fourth the pressures used by us. The higher pressures routinely employed in our studies may stimulate peristaltic waves of such intensity that smaller contractions are obscured or abolished. Records taken by our method at pressures comparable to those used by Carlson and Luckhardt presented irregular patterns—periods of complete phasic inactivity, occasional tonic or peristaltic contractions and small waves occurring about ten to twenty times a minute. Low pressures in the balloon system apparently provide an inconstant stimulus for esophageal motility, and motility records obtained at such pressures are undistinguished by any regular patterns. Higher intraballoon pressures that stimulate more consistent motility patterns seem to be preferable, consequently, in comparing the motor activities of the normal and abnormal esophagus.

PATIENTS

Records of esophageal motility were obtained in patients with cardiospasm, scleroderma and mechanical obstruction of the esophagus. An analysis of these records is given in Table II.

As might be expected the inflated balloon failed to pass into the stomach of the four patients with cardiospasm. In addition, however, esophageal motility was inadequate to carry the balloon from one part of the esophagus to the other. The tone was

TABLE II
ESOPHAGEAL MOTILITY IN PATIENTS WITH ESOPHAGEAL DISORDERS

Subject	Diagnosis	Tone (cc. of air in balloon)			Height of Wave (cc. of air expelled from balloon)			Frequency (No. of waves per minute)		
		Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower
J. K.	Cardiospasm	26	26-31	30	1-2	2-4	1-2	11	11	15
L. S.	Cardiospasm	..	35	35	..	7-10	3-6	..	10	13
W. W.	Cardiospasm	33	32	26	0	2-6	1-8	0	8	14
H. M.	Cardiospasm	..	21	19	..	13-32	10-32	..	4	10
G. R.	Scleroderma	33	37	28	0*	0*	0*	0*	0*	0*
P. H.	Scleroderma	20	28	26	0*	0*	0*	0*	0*	0*
M. H.	Scleroderma	21	19	27	0*	0*	0*	0*	0*	0*
J. L.	Scleroderma	..	16	26	..	0*	0*	..	0*	0*
O. F.	Carcinoma of stomach invading lower end of esophagus	20	22	26	11	12-18	13-15	6	4½	4½
J. O.	Stricture at esophagojejunal junction	6	13	15	3	18	14	7	4	6

* Very small waves occurring fifteen to twenty-four times per minute appear on the record, but these deflections are produced by respiration.

Cardiospasm. Studies of cardiospasm were made in the following patients:

W. W., a male aged seventy-two, had moderate to severe symptoms for two years. X-ray picture was typical of cardiospasm with 1 to 2+ dilatation and mild tortuosity of the esophagus. Cardia was dilated twice with only partial relief obtained.

J. K., a male aged fifty-seven, complained of vague abdominal symptoms. Cardiospasm was an incidental finding. X-ray showed 2 to 3+ dilatation of the esophagus with early "sigmoid" tortuosity of its lower portion. No treatment was necessary.

L. S., a female aged seventy, had symptoms for three years. There was 2+ dilatation of the esophagus with minimal tortuosity. Cardia was dilated twice with bougies but relief was transient.

H. M., a male aged twenty-three, had symptoms for one year. X-ray showed 1 to 2+ dilatation of the esophagus with no tortuosity. Treatment consisted of dietary methods.

diminished in all four patients. In two patients the wave pattern was strikingly decreased and demonstrated an irregular configuration. (Fig. 2.) The record of esophageal motility in patients L. S. and H. M. revealed strong phasic activity but the regular pattern of the normal esophagus was absent. (Fig. 2.) In spite of the difference apparent in their motility records, patients W. W. and J. K. on one hand, and L. S. and H. M. on the other presented similar clinical and roentgenologic manifestations.

As demonstrated by balloon-kymograph records it appears that esophageal motility in patients with cardiospasm has the following characteristics: (1) decreased tone, (2) phasic activity of variable intensity but irregular in configuration and (3) lack of propulsive capacity even if some phasic activity is present.

Scleroderma. Four patients with scleroderma were studied:

M. H., a female aged forty-five, had generalized severe scleroderma since 1941 with Raynaud's phenomena, skin changes and osteomyelitis of the terminal phalanges. There were minimal digestive symptoms. X-ray of the esophagus revealed slight dilatation with absence of all peristaltic activity.

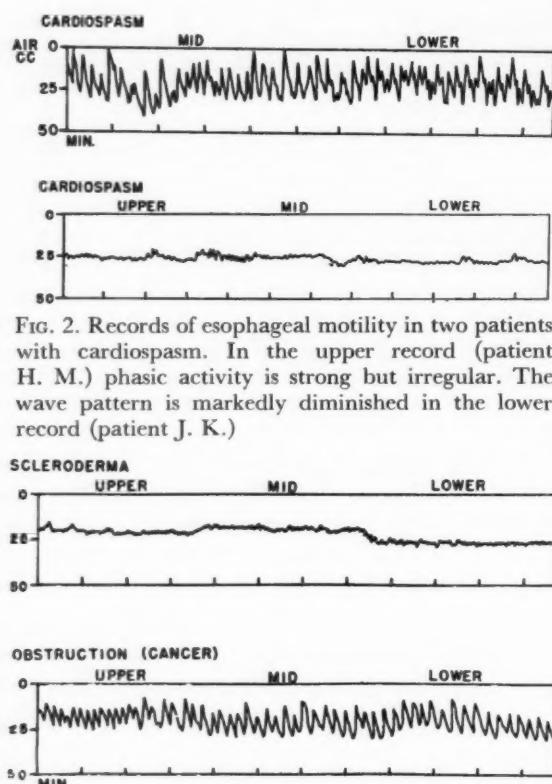


FIG. 2. Records of esophageal motility in two patients with cardiospasm. In the upper record (patient H. M.) phasic activity is strong but irregular. The wave pattern is markedly diminished in the lower record (patient J. K.).

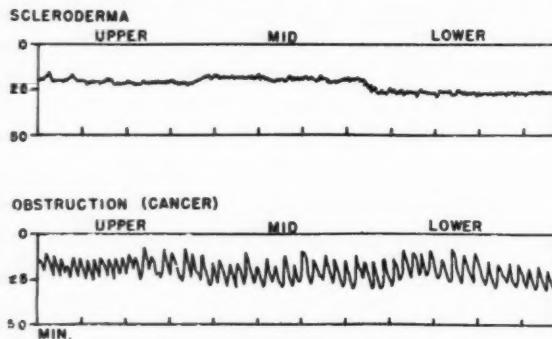


FIG. 3. Records of esophageal motility of patient M. H. with scleroderma (upper record) and of patient O. F. with mechanical obstruction of the esophagus (lower record).

P. H., a female aged fifty-three, had Raynaud's phenomena of the hands for three years. There were minor skin changes of the fingers and hands. Dysphagia, heartburn and diarrhea were pronounced. X-ray revealed moderate dilatation of the esophagus with absence of all peristaltic waves. The small intestine also showed marked hypomotility.

G. R., a male aged fifty-seven, had generalized scleroderma for ten years, with Raynaud's phenomena, skin changes and fibrosis of the lungs. There was occasional diarrhea but no dysphagia. X-ray showed moderate dilatation of the esophagus and absence of all peristaltic waves.

J. L., a female aged forty-three, suffered the onset of Raynaud's phenomena ten years ago. Skin changes which were typical of scleroderma started three and one-half years ago. No dys-



FIG. 4. Roentgenologic appearance of esophagus of patient O. F. The dilatation of the esophagus and the filling defect at its cardiac end can be observed.

phagia or other digestive symptoms were present. X-ray revealed stasis and absence of peristaltic waves in the esophagus but the caliber of the lumen was normal.

In these patients consistent abnormalities of esophageal motility were evident. Propulsion of the inflated balloon down the esophagus was slow or absent, but in one case (P. H.) the balloon slipped from the lower esophagus into the stomach after the patient swallowed. Motility records taken in each of the standard positions showed loss of tone and an absent or markedly diminished wave pattern. (Fig. 3.) It is noteworthy that the esophageal tone of these patients with scleroderma was exceedingly low as measured by the motility records although roentgenologic studies demonstrated only slight or moderate dilatation of the esophagus.

Mechanical Obstruction. Two patients with mechanical obstruction were studied:

O. F., a male aged fifty-three, previously had chronic pyloric obstruction from a duodenal ulcer and developed dysphagia. X-ray showed a moderately dilated esophagus suggest-

ing cardiospasm, but a defect near the cardia indicated neoplasm. (Fig. 4.) Further studies demonstrated carcinoma of the stomach with invasion of the lower esophagus.

J. O., a male aged fifty, developed symptoms of esophageal obstruction following total gastrectomy for cancer of the stomach. X-ray revealed narrowing at the esophagojejunal junction. Mechanical dilatation of that area ameliorated the dysphagia.

In these cases the balloon, after inflation in the upper esophagus, was carried down near the point of obstruction before its progress was arrested. The motility records showed a moderate decrease in tone but the wave pattern was striking in its amplitude and regularity. Although the roentgenologic appearance of the dilated esophagus in patient O. F. was somewhat suggestive of cardiospasm, his motility record showed none of the abnormalities found in this disorder. (Figs. 3 and 4.)

SUMMARY

Balloon-kymograph records of esophageal motility were obtained in subjects with and without clinical disorders of the esophagus. The motility recorded was that stimulated by inflating and maintaining a relatively large balloon in fixed positions of the esophagus.

In subjects without esophageal disorders a characteristic motility pattern was recorded in the upper, middle and lower esophagus, the middle and lower positions

presenting a regular sequence of large peristaltic waves.

In patients with cardiospasm the motility records demonstrated decreased tone and irregular phasic activity of variable intensity. Propulsion of the balloon along the esophagus did not occur.

In patients with scleroderma both tone and phasic activity were markedly diminished. Propulsion of the balloon was diminished but occasionally was present.

Esophageal motility in the presence of mechanical obstruction evidenced a mild decrease in tone and augmented regular phasic activity.

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II. Cardiospasm, A Generalized Disorder of Esophageal Motility*

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CURRENT concepts of cardiospasm lean heavily on the psychogenic aspects of this disorder, aspects that were mentioned as early as 1733 when Hoffmann¹ ascribed cardiospasm to "irrational love" and "uncontrolled desires." In spite of the venerability and popularity of the psychogenic theory, however, other hypotheses have had and still have their strong proponents. One group maintains that cardiospasm is the result of mechanical obstruction, whether by fibrosis,² by "liver tunnel,"³ by "diaphragmatic pinchcock"⁴ or by some other lumen-obliterating process. Another group, rather silent of late, favors the view that a primary esophageal atony is responsible.⁵ Perhaps most popular is Meltzer's⁶ idea,† seconded or re-conceived by Einhorn,⁷ Rolleston,⁸ Hurst⁹ and Alvarez,¹⁰ that a neuromuscular dysfunction prevents receptive relaxation of the cardia before an advancing peristaltic wave. The cause for such dysfunction has been found in congenital abnormalities,¹¹ nutritional deficiencies^{14,15} and emotional states.¹⁶⁻¹⁸

One reason for this plethora of contradictory hypotheses is the failure to define

† Hurst and Rake¹¹ stated that Meltzer, like von Miculiz,¹² ascribed cardiospasm to a "spasmodic contraction of the cardiac sphincter." Actually Meltzer⁶ wrote as follows, ". . . the cardia is under ordinary circumstances moderately contracted. At the beginning of swallowing, the cardia relaxes, . . . If the relaxing force were for any reason weakened or completely inhibited, the cardia would be considerably contracted in the non-swallowing phase (and would) not relax during the act of swallowing . . ." Thus he postulated a contraction of the cardia in his case because "the relaxing inhibitory force was suddenly weakened or completely abolished." These statements certainly embody the concept of Hurst's achalasia.

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the clinical condition usually known as cardiospasm. In some studies, for example, any esophageal spasms or any delays in the passage of material down the esophagus are considered as the equivalents of clinical cardiospasm. This practice ignores the findings of such experienced observers as Plummer and Vinson¹⁹ who separated their patients with "cardiospasm" into two groups: (1) those suffering from chronic if not continuous symptoms and manifesting some esophageal dilatation and (2) those with transient, irregular spasms, not necessarily located at the lower esophagus and not accompanied by luminal enlargement. A further separation of these two groups has been made by Templeton²⁰ who pointed out that cardiospasm is not only a disorder of the lower end of the esophagus but that the motility of the whole esophagus, as judged fluoroscopically and roentgenologically, is markedly deranged. As a matter of fact, Templeton has never seen a case of cardiospasm with normal esophageal motility.²¹ Our studies, which support and amplify Templeton's views, indicate that the clinical condition of cardiospasm can be defined more precisely and that it should not be confused with transient spasm, mechanical obstruction or other esophageal disorders.

Studies were carried out in four patients with cardiospasm, in four with scleroderma and in two with mechanical obstruction of the esophagus. Brief abstracts of these cases are given in our previous paper.²² In addition the following two patients were studied:

J. P. was a female aged thirty-one. A diagnosis of cardiospasm was made in 1945 following the onset of dysphagia in 1944. Periodic dilatation with bougies was done; there was relief of the symptoms for several months after each treatment. Raynaud's phenomena of the hands

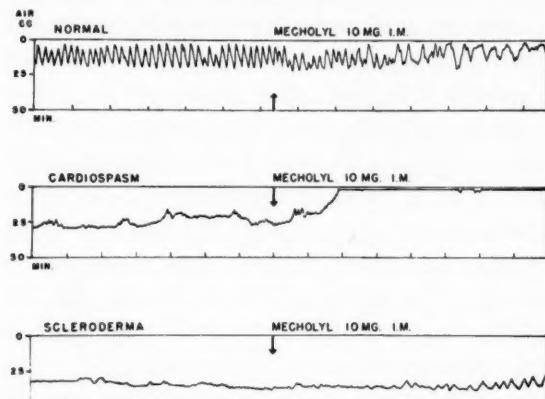


FIG. 1. Effect of 10 mg. of acetylbetamethylcholine chloride on esophageal motility. Upper record, control subject; middle record, patient J. K. with cardiospasm; lower record, patient G. R. with scleroderma.

began in 1945, accompanied by skin changes on the chest and back suggestive of scleroderma. X-ray of the esophagus at our hospital showed minimal dilatation, absence of all peristaltic waves and slight stasis.

R. F. was a male aged twenty-four. For two years the patient had transient and brief attacks of the sensation of food sticking in the lower esophagus; the sensation came on during periods of emotional tension. X-ray examination during an attack showed spasm of the esophagus 1 inch above the diaphragm. Peristaltic activity was normal and no dilatation was present. There were normal esophageal outlines and motility between the attacks.

In each of these cases the motility of the esophagus was studied by balloon-kymograph methods as well as by fluoroscopic and roentgenologic means.

As described previously,²² esophageal motility in cases of cardiospasm displays (1) decreased tone, (2) lack of propulsion and (3) an abnormal wave pattern. The phasic activity may be forceful or weak, but its configuration is irregular and even strong phasic activity is inadequate to propel the esophageal balloon. These changes occur in both the mid- and lower esophagus, areas where the normal esophagus exhibits strong

and effective propulsive waves. The motility pattern of cardiospasm is different from that found in other clinical disorders of esophageal motor function. In scleroderma the tone is depressed, as in cardiospasm, but phasic activity is practically absent. In

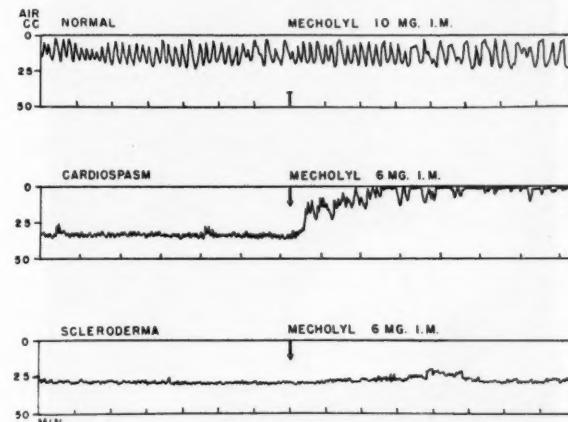
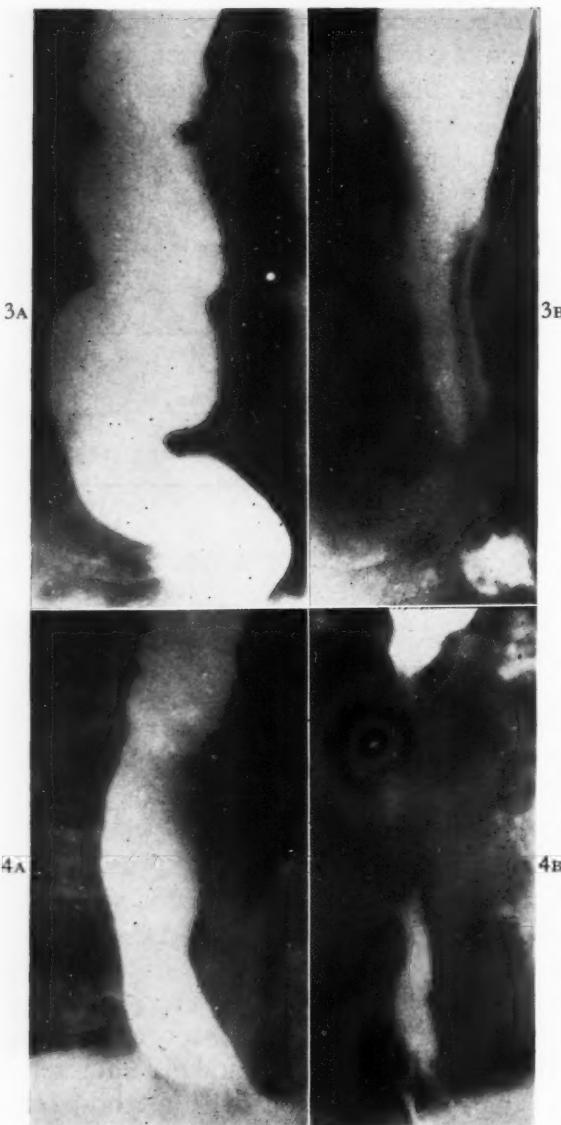


FIG. 2. Effect of acetylbetamethylcholine chloride on esophageal motility; 10 mg. given to control subject (upper record) and 6 mg. each to patient L. S. with cardiospasm (middle record) and patient P. H. with scleroderma (lower record).

mechanical obstruction of the distal esophagus large peristaltic waves of normal shape and arrangement may occur even if secondary dilatation proximal to the point of obstruction has taken place. The record of esophageal motility in patient R. F., with transient spasms of the lower esophagus, was normal in all respects and did not resemble that seen in patients with cardiospasm.

After suitable control records were obtained acetylbetamethylcholine chloride was given intramuscularly in 6 to 10 mg. doses to four control subjects, four patients with cardiospasm, two patients with scleroderma and patient J. P. The effect of this drug in patients with cardiospasm was startling for within two minutes of its administration a tonic, lumen-obliterating contraction of the esophagus took place. This contraction was of sufficient intensity to counteract a pressure of 20 cm. of water and to force all of the air out of the recording balloon. (Figs. 1 and 2.) The same effect could also be observed roentgenologically; after administration of acetylbetamethylcholine chloride even a considerably dilated esoph-



FIGS. 3A and B. Effect of acetylbetamethylcholine chloride on roentgenologic appearance of esophagus in patient J. K. with cardiospasm. A, before; B, three minutes after administration of 10 mg. of acetylbetamethylcholine chloride.

FIGS. 4A and B. Effect of acetylbetamethylcholine chloride on roentgenologic appearance of esophagus in patient W. W. with cardiospasm. A, before; B, three minutes after administration of 10 mg. of acetylbetamethylcholine chloride.

agus contracted to form a narrow lumen containing a thin thread of barium. (Figs. 3 and 4.) The tonic contraction, however, forced little material through the cardia. Instead, the esophageal content, whether a barium suspension or a recording balloon, was displaced backward into the upper esophagus. At the time of the tonic contraction the patient frequently experienced

substernal distress similar to the pain occasionally produced by the ingestion of food.

In normal subjects acetylbetamethylcholine produced some increase in tone but the effect was far less marked than that seen in patients with cardiospasm. (Figs. 1 and 2.) In patients with scleroderma the esophagus responded very little to injections of acetylbetamethylcholine; only minimal increases in phasic activity and tone were observed. (Figs. 1 and 2.) Patient J. P., who had been treated as a case of cardiospasm but who subsequently developed Raynaud's phenomena and skin changes suggesting scleroderma, responded to mecholyl as did the patients with clearcut scleroderma; that is, the esophageal motility evidenced very little alteration following injection of the drug.

COMMENTS

The number of patients studied is not large but tentative suggestions concerning the diagnosis and nature of cardiospasm seem permissible. The character of the esophageal motility record and the response to acetylbetamethylcholine appear to be sufficiently specific to differentiate at least a certain group of patients with cardiospasm from normal subjects and from patients afflicted with scleroderma, mechanical obstruction or transient spasms of the esophagus. This differentiation is not always simple by clinical and roentgenologic means. Cancer of the gastric cardia, for example, may produce a roentgenologic appearance of the esophagus that mimics cardiospasm closely. Our patient O. F., a case in point, exhibited a normal if hyperactive motility record, and it will be interesting to ascertain whether the motility records of all such patients are normal in contradistinction to the records of patients with cardiospasm. Finally, the response to acetylbetamethylcholine may provide a means of differentiating esophageal stasis produced by cardiospasm from that caused by scleroderma. Patient J. P. provides an example of a patient treated for cardiospasm, but the development of Raynaud's phenomena and

skin changes, as well as the negative esophageal response to parasympathetic stimulation, suggests that the correct diagnosis may have been scleroderma.

The motor abnormalities found in our patients with cardiospasm clearly involve both the mid- and lower esophagus, thereby indicating that the esophageal disorder in this condition is not merely confined to the cardiac end but that a motor dysfunction involves nearly the entire esophagus. The finding of abnormal wave patterns, which may be intense but so disorganized that propulsion is inadequate, can be accepted as strong evidence against the theories that cardiospasm is caused either by a primary neuromuscular atony of the esophagus or by some mechanical obstruction which produces secondary dilatation of the lumen. Furthermore, in our two patients with mechanical obstruction near the cardia, secondary dilatation was not accompanied by irregular phasic activity; on the contrary, the normal wave pattern was accentuated and augmented. No direct evidence either for or against the theory of achalasia is adduced by these studies. It would seem reasonable to postulate, however, that achalasia of the cardia is a feature of cardiospasm but that it represents only one abnormality in a neuromuscular dysfunction which involves nearly the entire esophagus.

The hypersensitive response to mecholyl evidenced by the esophagus in patients with cardiospasm can be advanced as another argument favoring the presence of a neuromuscular dysfunction in this condition. According to Cannon's law, destruction of a unit in a series of efferent neurons is followed by an increased irritability to chemical agents in the isolated structure or structures, the effect being maximal in the part directly denervated.²³ Viewed in light of this law the hypersensitivity of the cardiospastic esophagus to a parasympathomimetic agent suggests that the parasympathetic innervation of the esophagus has been disrupted somewhere along its course. Such a suggestion is in keeping with

the findings of those neuropathologists who maintain that a degeneration and decrease in the number of the intramural ganglia occur in cardiospasm.²⁴⁻²⁶ Whether a disorder of the parasympathetic nervous system is the primary or the only disorder responsible for cardiospasm remains to be seen. It is of interest, however, that spasms of the lower esophagus have been repeatedly described as one of the complications of vagal section carried out for the treatment of peptic ulcer.²⁷⁻³³ In our case, as well as in the other cases reported, the symptoms and findings subsided spontaneously within a few weeks. Unfortunately, motility records were not obtained in our patient with spasm of the lower esophagus following vagal section.

Although these studies indicate that cardiospasm is characterized by a generalized dysfunction of esophageal motility and that it may be produced by a disruption of the parasympathetic innervation, the ultimate cause of this condition remains obscure. That psychogenic stimuli may be responsible is consistent with the observations that have been made. On the other hand, since cardiospasm appears to be such a generalized esophageal disorder, it is questionable whether the production of isolated spasms in the esophagus, or of delays in swallowing time by the use of emotional stimuli can be used as arguments in favor of the psychogenesis of cardiospasm.^{34,35} The two conditions, namely, the clinical state of cardiospasm and isolated spasms of the esophagus appear unrelated to us. It may, of course, be argued that a gradual transition occurs from isolated spasms of the esophagus to well established cardiospasm³⁶ but such a transition is not generally described by experienced observers and, according to Vinson,^{29,37} probably does not occur. Further observations, however, will be necessary to settle this point.

Since the esophagus in cardiospasm appears to be hypersensitive to acetyl-beta-methylcholine, it is likely that it may also be hypersensitive to humoral agents

elaborated under conditions of emotional stress. The demonstration, therefore, that the symptoms of cardiospasm are accentuated by psychogenic stimuli can be accepted as evidence of the irritability and hypersensitivity of the esophagus in this condition, but it has relatively little validity as evidence purporting to show that cardiospasm is a psychogenic disorder. In this connection it must also be remembered that cardiospasm may be present as an asymptomatic condition as it was, for example, in our patient J. K. Hence, the frequent observation that the initial symptoms of cardiospasm may arise at the time of some emotional trauma is again of questionable etiologic significance. Such patients may well suffer from latent cardiospasm which is accentuated at the time of mental stress.

SUMMARY

In four patients with cardiospasm the esophageal motility as studied by balloon-kymograph records presented the following deviations from normal: decreased tone, lack of propulsion and irregular phasic activity of variable intensity. These abnormalities involved the lower two-thirds of the esophagus.

Administration of acetylbetamethylcholine chloride to patients with cardiospasm produced a violent tonic contraction of the lower half of the esophagus. This contraction obliterated even a considerably dilated lumen.

The esophageal motility pattern and the hypersensitive response to acetylbetamethylcholine chloride differentiated the esophageal motility of cardiospasm from that recorded in control subjects and in patients with scleroderma, mechanical obstruction of the esophagus and transient spasms of the esophagus.

The diffuse derangement of esophageal motility found in the patients with cardiospasm suggests that this disorder affects not only the cardia but nearly the entire esophagus. The hypersensitive response to a parasympatheticomimetic agent, when viewed in light of Cannon's law of denervation,

supports the hypothesis that disruption of the esophageal parasympathetic innervation plays a role in the pathogenesis of cardiospasm.

The observations made do not elucidate the ultimate cause of cardiospasm. They indicate, however, that cardiospasm should be more precisely defined and should not be confused with other disorders of esophageal motility. They furthermore indicate that some of the arguments which have been advanced in favor of the view that cardiospasm is a psychogenic disorder must be accepted with some reservation.

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Treatment of Chronic Non-specific Ulcerative Colitis with Aureomycin*

A Preliminary Report

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ALTHOUGH the primary etiologic agent is unknown, the secondary infection which develops when the mucosal barrier is broken^{1,2} greatly contributes to the clinical picture and the serious pathologic changes of this disease. No specific pathogen has been implicated despite attempts to prove an etiologic relationship with *Bacillus dysenteriae*^{3,4} or with *Diplococcus* of Bargen.^{5,6} Rather, a wide variety of organisms has been cultured from the stool, including hemolytic and non-hemolytic *Escherichia coli*, hemolytic and non-hemolytic streptococci, enterococci and *Staphylococcus aureus*.¹ In an attempt to combat this non-specific secondary infection which plays so important a part in ulcerative colitis, chemotherapy and antibiotics in various forms have been much employed. For this reason it seemed expedient to note the effects of a new and potent antibiotic, aureomycin.

Aureomycin, which was discovered by Duggar⁷ and his associates, is derived from the mold *Streptomyces aureofaciens* and possesses bacteriostatic and bactericidal activity for a number of gram-positive and gram-negative organisms, including some penicillin- and streptomycin-resistant organisms.⁸ It also possesses virucidal properties⁹ and we have reported favorably on its use in the treatment of lymphogranuloma venereum. Its toxicity is low, the lethal dose in mice being between 3,000 and 4,000 mg. per Kg. of body weight.¹⁰ In solution the hydrochloride salt is acid and intramuscular

injections may be irritating. It may be given intravenously in doses from 200 mg. to 1 Gm. in 500 cc. of 5 per cent glucose in distilled water. Oral administration of 250 or 500 mg. three or four times a day produces effective blood levels for twelve to thirty hours. Occasional nausea is encountered and may be alleviated or prevented with aluminum hydroxide.

We had obtained what seemed to be good results with aureomycin in a case of pyoderma gangrenosum occurring in a patient with chronic non-specific ulcerative colitis, the case having been previously reported.¹¹ The effects on the condition of the colon in this case were sufficiently impressive to warrant further study of the clinical effects of aureomycin in chronic non-specific ulcerative colitis.

PATIENTS, MATERIALS AND METHODS

The patients represented an unselected series and most of them had been under observation by one of us (J. A. M.) for long periods of time. All had been carefully studied by the usual methods of x-ray, sigmoidoscopy, stool culture and examination for parasites so that the diagnosis of idiopathic ulcerative colitis had been established to the exclusion of any other.

Aureomycin (as a hydrochloride) was given orally in 250 mg. capsules, one every eight hours. If after one or more weeks there was no change in the clinical course, the dose was doubled; or *per contra*, if in several weeks there was significant improvement, the dose was reduced to one capsule once or twice daily. No other drugs were used except occasional small doses of belladonna and phenobarbital. A low-residue bland diet was prescribed.

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Observations were directed solely toward the clinical response to the drug. These included, particularly, variation in the number of stools after treatment commenced, presence of blood in the stools, gain or loss in weight by the patient, variation in the sigmoidoscopic ap-

CASE I. H. M., was a male aged thirty-nine. The onset of diarrhea was in June, 1947, with ten to twelve movements daily. From then until the summer of 1948 he had seven to eight bowel movements a day and in October, 1948, they increased to fifteen and occasionally to twenty-

TABLE I
SUMMARY OF ACTIVE CASES OF ULCERATIVE COLITIS

No.	Name	Age	Sex	Duration of Disease	Duration of Treatment	Stools						After Treatment		
						No.		Blood		Character				
						Before Aureo-mycin	After Aureo-mycin	Before Aureo-mycin	After Aureo-mycin	Before Aureo-mycin	After Aureo-mycin	Weight Gained (pounds)	Well Being	Sigmoidoscopy Improved
1	H. M.	39	M	18 mo.	12 weeks	25	2	+	0	Watery	Formed	24	++++	+
2	E. K.	23	F	5 yr.	13 weeks	8	2	+	0	Watery	Formed	20	++++	+
3	J. C.	20	M	14 yr.	13 weeks	13	6	+	0	Watery	Formed	28	++++	+
4	L. M.	21	M	6 yr.	7 weeks	6	3	+	±	Soft	Formed	17	++	0
5	H. M.	19	M	12 mo.	11 weeks	7	2	+	0	Soft	Formed	25	++++	+
6	B. C.	42	M	18 yrs.	6 weeks	8	4	+	0	Soft	Formed	9	++++	+
7	E. G.	50	M	2 yr.	5 weeks	7	2	+	0	Soft	Formed	0	+++	0
8	J. A.	33	F	5 yr.	4 weeks	9	4	+	0	Watery	Formed	0	++	0
9	S. H.	42	M	1 mo.	12 weeks	3	2	+	0	Watery	Formed	4	++	+
10	R. R.	44	F	4 yr.	3 weeks	10	2	+	0	Watery	Semi-formed	-1	+	0
11	L. R.	45	M	5 yr.	11 weeks	6	2	+	0	Semisoft	Formed	0	+++	+
12	A. G.	32	M	12 yr.	9 weeks	9	5	+	±	Soft	Semi-formed	0	++	Not done
13	C. C.	28	F	1 yr.	5 weeks	8	3	+	0	Soft	Soft	-12	+	0

TABLE II
SUMMARY OF QUIESCENT CASES OF ULCERATIVE COLITIS

No.	Name	Age	Sex	Duration of Disease	Duration of Treatment	Stools						After Treatment		
						No.		Blood		Character				
						Before Aureo-mycin	After Aureo-mycin	Before Aureo-mycin	After Aureo-mycin	Before Aureo-mycin	After Aureo-mycin	Weight Gained (pounds)	Well Being	Sigmoidoscopy Improved
14	J. C.	38	M	18 yr.	9 weeks	3	3	+	±	Soft	Semi-formed	5	+	0
15	H. C.	28	M	11 yr.	7 weeks	2	2	+	±	Soft	Formed	8	+	+

pearance and, finally, subjective observations on the patient's sense of "well being." No studies were made on changes in the bacterial flora or in the roentgen appearance of the colon. These will appear at a later time.

CASE REPORTS

The significant clinical features of each case are briefly presented in the following histories and summarized in Tables I and II. In addition, several of the cases are presented graphically in Figures 1 to 9.

AUGUST, 1949

five or thirty daily. This was accompanied by a 25-pound weight loss. The past history includes an operation for perforated peptic ulcer in 1930, an undiagnosed hemorrhage from the rectum in 1939, an appendectomy in 1946, a subtotal gastrectomy in November, 1946, with recurrence of ulcer symptoms early in 1947, for which vagotomy and splenectomy were performed.

He was admitted to Harlem Hospital on November 18, 1948, at which time he was having as many as twenty-five bowel movements

daily. Aureomycin, 250 mg. every eight hours, was given and on his discharge three weeks later the movements averaged two daily. Following discharge aureomycin was discontinued and the movements increased to three or four a day. When aureomycin was resumed, the stools be-

averaging seven to eight bowel movements a day. Aureomycin, 250 mg. every eight hours, was given and continued until discharge from the hospital on December 1, 1948, when she was having two formed bowel movements daily without blood. Sigmoidoscopy revealed an almost normal colon. After being without aureomycin for two weeks her bowel movements increased to four a day but were promptly reduced to one or two daily upon resumption of the drug. Proctoscopy on January 13, 1949, revealed an entirely normal mucosa. Aureomycin was discontinued and the movements increased to four soft stools daily but returned to two formed movements when 250 mg. of aureomycin were given daily for one week. Aureomycin has been discontinued and the stools remain formed and occur twice daily.

CASE III. J. C., a male aged twenty, has had diarrhea since 1934 when, at the age of five, he first had ten to twelve bowel movements a day containing pus, blood and mucus. He was fairly well until about 1941 when he again began to have diarrhea and had numerous recurrences until 1942 when he developed a fistula in ano. From 1943 to early 1947 he averaged about six movements a day. In the spring of 1947 his bowel movements increased to eight or nine daily. This increase continued so that when first seen on August 8, 1948, he was having thirteen bowel movements a day. A barium colon enema done in 1943 showed ulcerative colitis and x-ray studies in August, 1948 confirmed this diagnosis. Repeated sigmoidoscopies showed severe chronic ulcerative colitis.

Aureomycin, 250 mg. every eight hours, was commenced on December 4, 1948, and in one week caused a decrease in the number of bowel movements from thirteen to seven daily. On January 21, 1949, aureomycin was increased to 1,500 mg. daily, and in the following week stools averaged six per day. He was kept on this regimen until February 19th, during which time there was no significant change when aureomycin was reduced to 750 mg. a day. On this dosage he averaged about four movements daily, all without blood, "feels better than ever before" and has gained 28 pounds since initiation of aureomycin therapy. He was particularly gratified by his improvement since it took place while he was carrying a heavy program at college which was not interrupted during final examinations, at which time in the past he always had had an exacerbation of the disease.

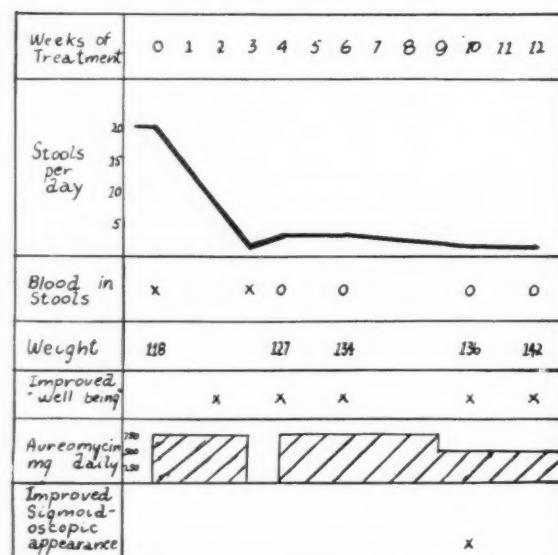


FIG. 1. Case I. H. M., male, thirty-nine years old.

came formed again and were reduced to two daily, with a dose of 750 mg. daily. The movements continued to be formed and remained at two daily when aureomycin was reduced to 250 mg. twice a day in the tenth week of treatment.

Sigmoidoscopy prior to his hospitalization showed a swollen congested mucosa. When sigmoidoscopy was repeated on January 21, 1949, the rectum and lower sigmoid colon showed no abnormalities. His weight increased from 118 to 142 pounds.

CASE II. E. K., was a female aged twenty-three. The onset of diarrhea in 1943 was associated with some bleeding, averaging six to eight movements daily. This continued on and off to date and was usually aggravated by an emotional disturbance. Barium colon enema in May, 1944, indicated chronic ulcerative colitis involving the entire colon and repeated sigmoidoscopies showed findings typical of this condition. In March, 1948, she had a complete check-up at Mercy Hospital, Rockville Center, where the diagnosis of colitis was again established. Proctoscopic examination in October, 1948, showed typical granular ulcerating, congested, bleeding mucosa.

The patient was admitted to Harlem Hospital on November 10, 1948, at which time she was

CASE IV. L. M., a male aged twenty-one, was first seen in 1942 at the age of fourteen when he was having twelve bloody movements daily associated with fever and chills. In the last six years he averaged six soft, frequently bloody

movements daily, despite a severe cold which (as just noted) usually aggravated his diarrhea. He had no pain and there was less blood in the stool. He had gained 17 pounds in weight in seven weeks.

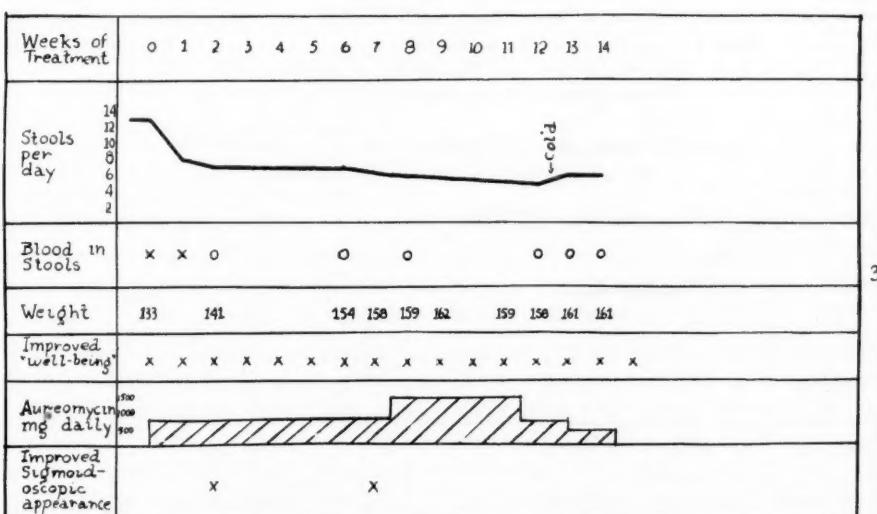
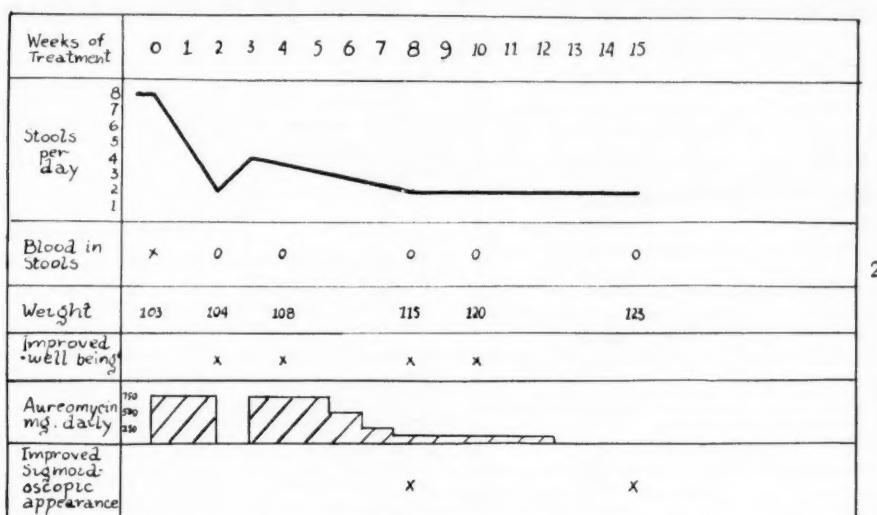


FIG. 2. Case II. E. K., female, twenty-three years old.

FIG. 3. Case III. J. C., male, twenty years old.

movements a day. Recently there has been considerable weight loss and blood in every movement. Whenever he had a common cold, movements increased to twenty daily. Sigmoidoscopy on January 15, 1949, revealed diffuse congestion, many small bleeding points and, at 1 and 5 inches from the anus, small, flat polypoid growths. At this time he was given aureomycin, 250 mg. every eight hours.

During the first three weeks there was little change either in bowel movements or subjective sensation but in the fourth week he showed definite improvement, with two to three soft

CASE V. H. M. was a male aged nineteen. The onset of bloody stools was in October, 1947. In December, 1947, barium enema revealed chronic ulcerative colitis. About this time his bowel movements increased to eight daily, and he was admitted in January, 1948, to the Israel Zion Hospital (Brooklyn), where the diagnosis was confirmed, for intravenous feedings. Aureomycin therapy was initiated on December 11, 1948, at which time he was having seven mushy, bloody movements daily. Sigmoidoscopy showed a granular, congested, easily bleeding mucosa.

The following week his movements were

formed and reduced to three daily without blood. Aureomycin has been continued and he now averages two movements a day without blood. Sigmoidoscopic examination on January 22, 1949, revealed no congestion or edema but there was an occasional bleeding point. On

revealed a normal mucosa up to 7 inches. His weight increased from 127 to 153 pounds. He is now carrying a full college program and states that he feels "wonderful."

CASE VI. B. C. was a male aged forty-two. For the past eighteen years the patient has had

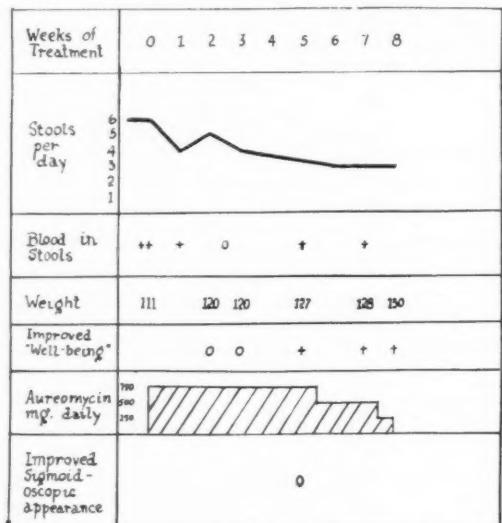


FIG. 4

FIG. 4. Case IV. L. M., male, twenty-one years old.

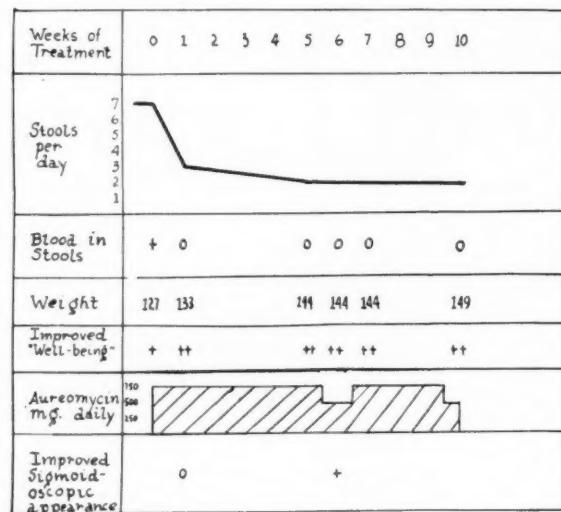


FIG. 5

FIG. 5. Case V. H. M., male, nineteen years old.

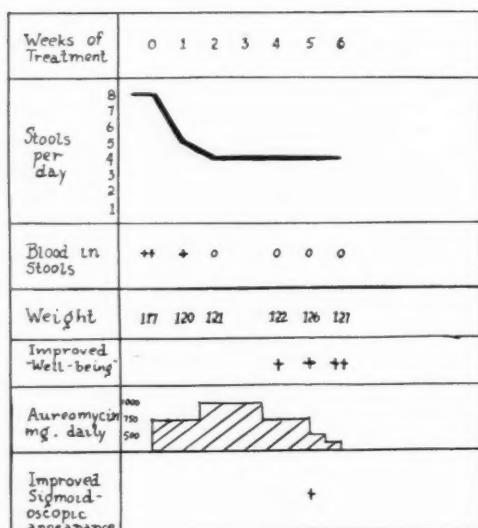


FIG. 6

FIG. 6. Case VI. B. C., male, forty-two years old.

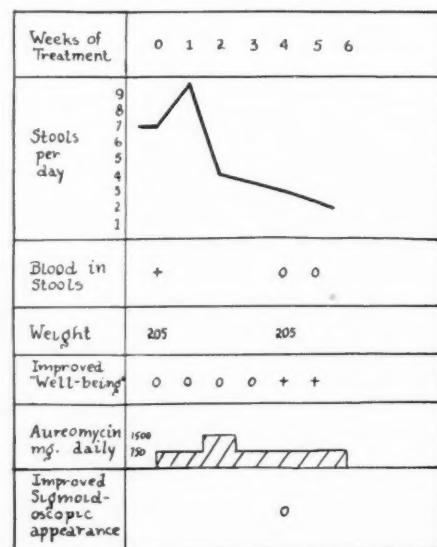


FIG. 7

FIG. 7. Case VII. E. G., male, fifty years old.

February 19, 1949, aureomycin was reduced to 500 mg. daily and one week later to 250 mg. daily. The movements continued to be well formed, without blood and average two daily. He was free from any pain or tenesmus which had previously been a most troublesome symptom. Sigmoidoscopy on February 27, 1949,

annual bouts of bloody diarrhea lasting three months. Repeated sigmoidoscopies and barium enemas revealed typical findings of ulcerative colitis. During the last seven years he was having about eight soft, bloody movements daily but stated that his true bowel habit would be about twelve to fourteen stools a day were it not for the

Tr. Opii which he had been taking steadily. This was discontinued and aureomycin, 250 mg. every eight hours, was given beginning January 22, 1949. On January 29, 1949, the bowel movements were five a day, slightly more formed and with less blood. Aureomycin was increased to

tremely congested, edematous bleeding mucosa with a thick purulent discharge. Aureomycin, 250 mg. every eight hours, was started. Four days later he again had a cold and the stools increased to ten daily. Aureomycin was increased to 1,500 mg. daily. In the next three to

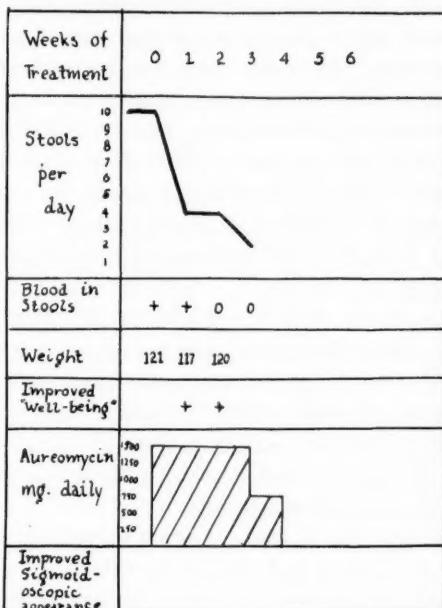


FIG. 8

FIG. 8. Case x. R. R., female, forty-four years old.

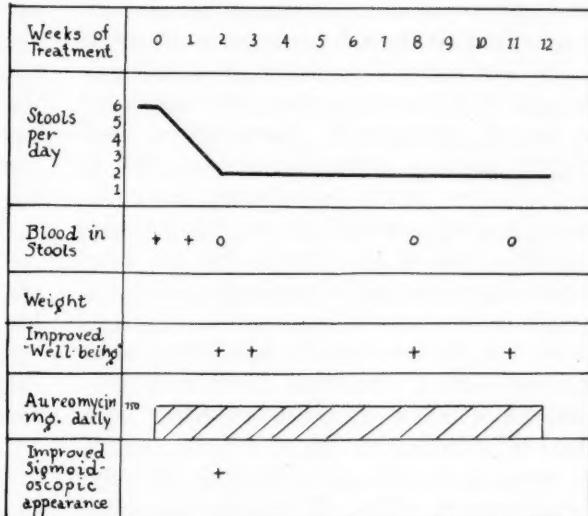


FIG. 9

FIG. 9. Case xi. L. R., male, forty-five years old.

1,000 mg. a day. During the next three weeks he felt better and was having three to five semi-formed movements daily, free of blood. Aureomycin was reduced to 750 mg. daily. The stools continued at four daily, were fairly well formed and free of blood. Subjectively he felt much stronger, was free of tenesmus, had had no "accidents" and was 9 pounds heavier. Sigmoidoscopy on February 27, 1949, showed moderate congestion but no bleeding points, edema or ulceration. Aureomycin was decreased to 250 mg. daily.

CASE VII. E. G. was a male aged fifty. In February, 1946, following a cold, he had four to seven watery bowel movements a day, with blood and mucus. Since then, he has had frequent attacks of diarrhea with as many as fifteen to twenty movements a day. He believes the attacks of diarrhea are usually initiated by nervous tension. Repeated sigmoidoscopic examinations and barium enemas revealed typical findings of chronic ulcerative colitis.

About January 10, 1949, he had a cold and had six to eight bloody movements a day. Proctoscopy on January 21st revealed an ex-

four days the movements were reduced to six to eight and in the course of the following two weeks the bowel movements gradually diminished so that on February 15, 1949, he was having two or three formed stools a day. At this time aureomycin was discontinued for three days and the bowel movements promptly increased to five a day. When aureomycin was resumed (750 mg. daily), he again had two formed stools daily. There has been no change in the sigmoidoscopic picture.

CASE VIII. J. A., a female aged thirty-three, developed bloody diarrhea in March, 1943, and was hospitalized at the Mount Sinai Hospital for three months, receiving fifteen transfusions. Severe recurrence for five weeks in November, 1944, and again in February, 1947, necessitated hospitalization. When first seen on August 9, 1947, she was having six soft, bloody stools daily. Sigmoidoscopic examination was typical of ulcerative colitis, as was the roentgen examination which revealed, in addition, a complete situs inversus. Since the initial visit, she has had severe recurrences requiring further hospitalization, each recurrence lasting several weeks to

months. On February 12, 1949, there was a sudden onset of diarrhea with nine bloody movements daily. Aureomycin, 250 mg. every eight hours, was prescribed. Four days later the stools were reduced to four a day, without blood. This continued for ten days when the movements became formed and were only two in number. Between March 1st and 4th, she took no aureomycin and continued to feel well. On the latter date she began to menstruate; she also developed a cold and had six bowel movements. Aureomycin, 250 mg. every eight hours, was ordered and on each of the next two days she had eight bloody bowel movements. Aureomycin was increased to 500 mg. every eight hours with a gradual reduction in the bowel movements as well as a disappearance of blood. During the course of this episode the patient did not lose weight and sigmoidoscopic examination showed no change.

CASE IX. S. H. was a male aged forty-two. This patient had a duodenal ulcer with obstruction, for which a gastro-enterostomy was done in 1945. In November, 1948, he began having three soft, watery, frequently bloody bowel movements daily. Previously he had always had one or two formed movements. He attributed the diarrhea to increased nervous tension and worry over his son who was a mental problem. A barium colon enema and proctoscopy on December 4, 1948, were both positive for chronic ulcerative colitis. On December 8, 1948, aureomycin, 250 mg. every eight hours, was initiated. After one week the bowels became formed, were reduced to two daily and the blood became less and less until it was entirely absent. After six weeks aureomycin was reduced to 250 mg. twice each day with no alteration in bowel habits. Sigmoidoscopy on February 5, 1949, showed a few pin-point bleeding areas but no ulcers, edema, congestion or friability. Aureomycin was reduced to 250 mg. daily and on February 20, 1949, was discontinued. The movements continued to be formed, two daily (his previously normal bowel habit) and without any blood. During the time he was on aureomycin his weight increased from 161 to 165 pounds.

CASE X. R. R. was a female aged forty-four. In 1944 this patient had bloody diarrhea with fifteen to twenty movements daily, the attack lasting about four months. In November, 1948, she had twenty bowel movements each day for one month, which gradually became less, so

that for the next two months there were about ten stools a day containing much blood, pus and mucus. X-ray examination on February 15, 1949, revealed typical severe ulcerative colitis with polyp formation. Proctoscopy revealed profuse bloody purulent discharge, with an ulcerated, edematous and bleeding mucosa. The liver was 2 inches below the costal margin and tender, and there was marked edema of the ankles. She was hospitalized at the University Hospital (New York) where her temperature fluctuated up to 101°F. Laboratory study disclosed the liver function tests to be normal but marked anemia and hypoproteinemia were present (7.7 Gm. of hemoglobin; total protein 4.7 Gm.).

Aureomycin, 500 mg. every eight hours, was started and after one week the stools were reduced to four in twenty-four hours, all with less blood. At the end of the third week of treatment the patient had two formed movements daily, without blood, pus or mucus, and the ankle edema had subsided.

CASE XI. L. R. was a male aged forty-five. About five years ago this patient had an attack of diarrhea, cramps and fever lasting one week. In 1945 he had a recurrence of the diarrhea, with bleeding, which persisted to November 27, 1948, when he was first seen. His stools averaged five to six semisoft movements with varying amounts of blood, from specks to half teaspoonsfuls. Preceding each movement there was a mucous discharge. Sigmoidoscopy revealed an edematous hyperemic mucosa which was the seat of geographic erosions. There was much bleeding with considerable lymphoid hyperplasia and mural fibrosis. Cultures were negative for *B. dysenteriae*. Aureomycin, 250 mg. every eight hours, was commenced on November 27, 1948. For two weeks he continued to pass some mucus and a little blood but no pus. The stools gradually became less frequent so that he had two or three formed movements daily without tenesmus, pus or blood. There was improvement in mood, he became brighter, more cheerful and less irritable. Sigmoidoscopic examination on December 11, 1948, showed an occasional pin-point bleeding area but no ulcerations. He continued to report further improvement and aureomycin was discontinued on February 15, 1949, after eleven weeks.

CASE XII. A. G. was a male aged thirty-two. In 1937 this patient began to have diarrhea while he was a student at college. The move-

ments fluctuated between four and twelve stools daily. He continued to have frequent bowel movements and was studied in 1941 and 1942 when barium enema showed an "extensive ulcerative colitis involving the entire large bowel." Similar findings were noted in later barium enemas and repeated sigmoidoscopies always showed typical ulcerative colitis findings. For the past several years he has averaged eight or nine soft bloody movements a day. Aureomycin, 250 mg. every eight hours, was started on December 22, 1948, and was continued four weeks with reduction of stools to five daily. At this time aureomycin was increased to 500 mg. twice daily. This produced no change in the stools but two weeks later the patient reported (by mail): "I now feel better than usual. The consensus is that I am looking well—for me."

Aureomycin was now dropped to 250 mg. every eight hours and two weeks later a similar report was received from the patient.

CASE XIII. C. C. was a female aged twenty-eight. For the past year this patient had from five to ten bowel movements daily containing blood and pus with tenesmus and urgency. Cramps were relieved by bowel movements. She was admitted to Harlem Hospital on January 15, 1949, where sigmoidoscopy showed an edematous and friable mucosa with small hemorrhagic areas and a purulent discharge. Barium colon enema revealed loss of haustration with diffuse irregularity of the outline of the descending colon. Aureomycin, 250 mg. every eight hours, was given on February 3, 1949, and was increased to 500 mg. every eight hours on February 8, 1949. The bowel movements were reduced to three daily, were more formed and contained less blood. Cramps continued and nausea developed. Aureomycin was reduced to 250 mg. every eight hours on February 19, 1949, and on this regimen she continued to have three to four soft bowel movements daily. Her weight dropped 12 pounds during the month. There was no change in the sigmoidoscopic picture.

CASE XIV. J. C. was a male aged thirty-eight. In this patient the onset of diarrhea was in 1931 with several attacks every year since. In 1935 blood was first noticed in the stool. Attacks recurred two or three times a year until 1939. From then on he was fairly well until 1945 when he had four to five bowel movements a day associated with considerable weight loss. In May, 1947, bowel movements increased to ten loose stools a day and this condition was ag-

gravated when he went away on a vacation. During the winter of 1947 to 1948 there was considerable diarrhea and he had "accidents" on the way to work so that he became quite nervous about going to his office. Repeated sigmoidoscopic examinations over these years revealed typical findings of chronic ulcerative colitis and a polyp 2 inches from the anus.

Aureomycin, 250 mg. every eight hours, was started on December 16, 1948. On January 17, 1949, he noted little improvement so the dose of aureomycin was increased to 500 mg. every eight hours. He remained on this regimen for three weeks after which he became so nauseated that he discontinued the drug. The bowel frequency was about the same (three to four) as before treatment but the stools were somewhat more formed and contained less blood. He felt stronger, had gained 5 pounds (115 to 120) and had had no "accidents," which heartened him a great deal.

CASE XV. H. C. was a male aged twenty-eight. In this patient the onset of diarrhea was in 1938, with frequent recurrences in 1940 and 1941, each with about eight or nine bowel movements a day. He was studied at the Roosevelt Hospital where a barium colon enema showed "atypical mucous membrane throughout the large bowel. There is definite ulceration of the transverse colon and descending portion." Although relatively well in the period of 1942 to 1947 there were occasional bouts of diarrhea, frequently with blood. Repeated sigmoidoscopic examinations revealed typical findings of ulcerative colitis. In September, 1947, he developed an ischiorectal abscess which required drainage and subsequent re-operation. During 1948 he averaged two semiformal bloody stools daily. Sigmoidoscopy on December 17, 1948, showed diffuse mucosal congestion with edema and many small bleeding points. Aureomycin, 250 mg. every eight hours, was given. On January 10, 1949, the patient stated that the stools had become very well formed although still containing slight blood. Sigmoidoscopy on this same date to 8 inches revealed normal mucosa. Aureomycin was reduced to 250 mg. twice daily. On February 4, 1949, bowel movements were well formed and numbered two daily containing somewhat less blood. Sigmoidoscopy again revealed normal mucosa. A weight gain of 8 pounds was noted.

A case of special interest, not included in this series, is reported from the Mount Sinai Hos-

pital. Aureomycin was requested by Dr. Burrill B. Crohn for use in treatment of one of his patients and an abstract of the protocol is as follows: A thirty-eight year old male (W. F.) entered the Mount Sinai Hospital on January 7, 1949. He had had recurrent exacerbations of chronic ulcerative colitis during the past twelve years. Three weeks before admission an acute exacerbation developed in which he had five to ten watery and bloody bowel movements daily accompanied by severe rectal tenesmus and fever. On admission he showed marked secondary anemia, a temperature of 102°F., pulse 100 and respiration 22. Laboratory studies revealed a hemoglobin of 12.9 Gm. This value varied according to transfusions and blood loss per rectum. The white blood count was 23,500 and the differential showed a shift to the left.

Under treatment with amphetamine and deodorized tincture of opium he continued to have five or six watery bowel movements daily. From January 10th to the 19th he was given 2 Gm. of streptomycin daily in divided doses intramuscularly but despite this therapy his bowel movements averaged twenty daily. Bowel movements were foul in odor, containing pus, blood and mucus. On January 20th and 21st he was given 300,000 units of penicillin daily with no effect. On January 19th his condition had deteriorated showing abdominal distention and tenderness and spasm in the right lower quadrant associated with singultus and vomiting. A surgical consultant decided against surgical intervention and the patient was treated conservatively with nothing by mouth and a Harris tube. On January 21, 1949, it was deemed advisable to use aureomycin.

Treatment was initiated with intravenous administration of 600 mg. of aureomycin in divided doses and 250 mg. orally four times a day. The oral route was employed despite the fact that some of the drug would be lost through the Harris tube. At the beginning of treatment his temperature was 102°F., pulse 130 and abdominal distention was present with marked tenderness on the right side. Thirty-six hours later the temperature fell to normal but rose again to 101°F. on the fifth and sixth days after treatment was started. On the sixth day of aureomycin therapy the temperature fell to normal and remained normal thereafter. During this period there was a distinct change in the character of the bowel movements. On an average there were eleven bowel movements per day.

Some were semiformed, non-odorous, containing no pus and little or no blood. The color also changed from green to light yellow. On February 1, 1949, the patient was placed on oral aureomycin alone, receiving 250 mg. four times a day and his condition was definitely improved. At this time an ileostomy was decided upon and on February 3, 1949, it was carried out. Operation revealed "evidence of acute and chronic inflammation of the right lower quadrant with the terminal ileum adherent to the cecum. There was also an inflammatory process in the pelvis. These processes were probably due to a recent perforation." Postoperatively, the patient continued on intravenous aureomycin for the first forty-eight hours during which time he had the usual postoperative reaction. However, on the second postoperative day the temperature increased to 103.8°F. with a pulse to 134. Bowel movements became bloody, increased in frequency and the patient went rapidly downhill and expired on February 11, 1949.

RESULTS

The fifteen cases constituting this study may be divided into two groups: (1) Thirteen cases representing "active" colitis (i.e., diarrhea of from three to twenty-five bowel movements daily with typical sigmoidoscopic and roentgen findings) and a second group (2) of two cases (xiv and xv) which at the time of study were in a "quiescent" phase (although still displaying roentgen and sigmoidoscopic evidence of disease and with a history of repeated earlier bouts of severe activity).

Active Cases. Bearing this division in mind, it is immediately apparent that the greatest effect occurred in the diarrheal group (1) of which all thirteen patients showed a reduction in the number of daily stools. This reduction amounted to at least 50 per cent in eleven of the thirteen cases. The majority of cases (I, II, III, V, VII, VIII, X, XI and XIII) exceeded this reduction and were having one-third, one-fourth, or even fewer movements than before initiation of aureomycin.

There were two cases (of thirteen) in which stools were reduced but by less than one-half. In one of these (Case XII) the colitis

history extended twelve years and the movements had been "stabilized" at about nine daily. These were reduced in about four weeks to five per day. The second case (Case ix) was a colitis of brief duration (one month) with minimal symptoms, and the patient's bowel habit was restored to the "pre-colitic" normal (two) after one week of aureomycin.

Gross blood was present in the stools of all thirteen patients. As treatment progressed it disappeared completely from eleven (85 per cent) and was reduced in amount and/or frequency in the remaining two patients.

A change in the consistency of stools was also observed. All of the thirteen patients had watery or semiformal stools before commencing aureomycin therapy. Of these, ten (77 per cent) later had formed stools and in two more the stools became gradually firmer although never fully formed. Thus, concomitant with the reduction in diarrhea, twelve of the thirteen patients (92 per cent) developed improved consistency of the stools.

Along with the reduction of bowel movements there was a gain in weight in seven patients (of thirteen) ranging from 4 to 28 pounds. The patients displaying the most severe degree of nutritional deficiency manifested, in general, the greatest degree of recovery while those who had maintained their weight despite the disease showed only little (Case ix) or no improvement in this respect.

Two patients, although showing reduction in diarrhea, lost weight. In the first case (Case xiii) this was in large part due to nausea which developed incident to use of the drug, the weight loss being promptly reversed when nausea was controlled by use of aluminum hydroxide gel. The second patient (Case x) lost about 3 pounds in the first two weeks of hospitalization, apparently due to disappearance of marked ankle edema, when the hypoproteinemia was relieved.

General well being kept pace with reduction in bowel movements and weight gain.

AUGUST, 1949

Practically all of the patients in this group said they felt much better and stronger.

Seven of twelve patients showed improvement in the sigmoidoscopic appearance. This took the form of reduction in congestion and edema, decrease in bleeding points and ulcers and less granular appearance of the mucosa. In some cases the sigmoidoscopic picture was normal.

The improvements reported were obtained in some of the patients within a week or two but often the maximum benefit was not achieved for three to five weeks or longer. Aureomycin was continued well beyond this time whenever possible so that the value of a prolonged course of antibiotic therapy could be determined.

Quiescent Cases. As was to have been expected the patients in the quiescent group (2) showed no change in the number of their bowel movements. But even here certain benefits were reported. Case xiv, a very undernourished thirty-eight year old male weighing 115 pounds, gained 5 pounds and stated that he felt better despite marked nausea which forced him to discontinue the drug. In addition, the stools had become more formed and he no longer had "accidents." There was no change in the appearance of the bowel on sigmoidoscopy. Case xv gained 8 pounds in weight, reported slightly less blood in the stools which had become well formed and showed some improvement in the sigmoidoscopic picture.

Toxic Effects and Side Reactions. No toxic effects or side reactions were observed in this series of cases other than nausea. This was noted in three of the fifteen patients. J. C. (Case xiv) became so nauseated after 1,500 mg. daily for three weeks that he had to discontinue the drug. Case xiii continued to take the drug despite marked nausea, which resulted in anorexia and weight loss. The nausea was controlled when aluminum hydroxide gel was administered simultaneously with aureomycin and the dosage of the drug was reduced.

Evaluation. The difficulty in determining the value of any therapy in ulcerative colitis is well known. No disease has more

of a tendency toward natural, spontaneous remission, often occurring suddenly just when the picture seems blackest. The powerful effect of psychologic influences, such as the exhibition of a new therapy, is also well known. The greatest caution must therefore be exercised in imputing a specific virtue to any therapy in this disease. We believe, however, that the high degree of response to aureomycin obtained in these unselected cases is encouraging and significant and deserves further study.

SUMMARY AND CONCLUSION

1. Thirteen patients with active ulcerative colitis were treated with aureomycin hydrochloride* in doses averaging 250 mg. every eight hours. All showed reduction in the number of bowel movements; in eleven of the thirteen cases (85 per cent) this reduction amounted to 50 per cent or more.
2. In eleven of the thirteen cases (85 per cent) the gross blood in the stools disappeared.
3. All of the thirteen active patients reported improvement in the sense of well being (including greater strength, less pain and tenesmus and cessation of accidents).
4. Gain in weight (4 to 28 pounds) was reported in seven patients (54 per cent) during treatment. Weight loss occurred in two hospitalized cases.
5. The sigmoidoscopic appearance was improved in seven of twelve patients.

* The aureomycin used was furnished through the courtesy of the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, N. Y.

6. Two patients with quiescent ulcerative colitis showed no change in daily bowel movements but reported improvement in well being, less blood in the stools and a weight gain of 5 and 8 pounds, respectively.

7. Severe nausea was experienced by three patients. This was controlled by aluminum hydroxide gel and reduction in dosage.

8. While the results herein reported are most encouraging and appear significant, great caution is urged in interpreting the value of aureomycin in ulcerative colitis therapy.

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Significance of Hyperalimentation in Treatment of Chronic Idiopathic Ulcerative Colitis*

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UNTIL two and one-half years ago our management of patients with chronic idiopathic ulcerative colitis, like that of many other clinics, consisted of: (1) a high caloric, low residue diet of which the patient ate very little; (2) a course of some sulfonamide, despite the fact that a pathogenic bacterium rarely, if ever, was isolated from the stool; (3) vitamins and (4) various antidiarrheal agents. When the patient failed to respond to these measures, he was referred to a surgeon for an ileostomy.

Then we tried a "medical ileostomy," the purpose of which is to place the colon at rest. This was accomplished by intubating the small intestine as far as the terminal ileum (or if the ileum was involved, to a point just proximal to the involved portion) with a Miller-Abbott tube and by applying constant suction so as to prevent the small intestinal contents from entering the diseased bowel. At the same time an effort was made to maintain the nutritional status of the patient by oral administration of a large quantity of a mixture of predigested casein and dextrimaltose in such solution that any residue could be withdrawn through the tube. The results were most satisfactory.

Our experience over a year with this procedure led us to suspect that the more effective factor in the improvement of the patient was the accomplishment of adequate nutrition by administration of the

hydrolysate-dextrimaltose solution. Therefore in a subsequent series of cases we omitted the intubation but retained all the other features of the adopted management: administration of an excessive amount of a readily absorbable dietary solution, high in protein and with added vitamins, blood transfusions when indicated and measures for the control of emotional disturbances. Chemotherapeutic agents and antibiotics were rarely employed.

Our experience with fourteen patients who had chronic non-specific ulcerative colitis so treated, compared with that of a series of patients who underwent intubation, comprises the basis of this report.

PROCEDURE

The patient was placed on a dietary regimen that consisted solely of administration of a solution of a mixture of equal parts of an enzymatic casein hydrolysate* and of dextrimaltose. A measured amount of the mixture, sufficient for a day's feedings and calculated on the basis of 20 calories per pound of pre-illness weight, was dissolved in enough boiling water to yield a 15 to 25 per cent solution and stored in quart milk bottles in an ice chest. Two hundred to 400 cc. of the solution were ingested every two hours from 6 A.M. to 10 P.M., thus supplying 225 to 450 Gm. of protein and 1,800 to 3,600 calories daily. In addition the patient received iron and the following vitamin

* The powder mixture, consisting of 50 per cent protolysate and 50 per cent dextrimaltose No. 2, was generously supplied by Mead Johnson and Co.

* From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Hyperalimentation for Ulcerative Colitis—*Machella*

supplements by mouth: thiamine, 10 mg., nicotinamide, 100 mg., riboflavin, 2 mg. and ascorbic acid, 50 mg. three times per day and 1 multivitamin capsule and 2 mg. of vitamin K daily. Administration of the solution was continued until such time as clinical and sig-

half months pregnant. The terminal ileum, in addition to the colon, was involved in four patients.

The average loss of weight prior to the onset of therapy was 20 (6 to 34) pounds, and the number of stools ranged from an average

TABLE I
DESCRIPTION OF PATIENTS

Case No.	Sex/Age	Duration*		General Physical Appearance	Fever	Anorexia
		Of Disease	Of Immediate Attack			
1	M/13	2 Y*	2 M	Critical	+	+
2	M/29	2 Y	3 M	Good	0	+
3	F/60	4 Y	7 M	Good	0	+
4	F/21	19 M*	6 M	Good	0	0
5	M/25	11 Y	1 M	Good	+	0
6	M/22	8 Y	4 Y	Poor	+	+
7	M/60	4 Y	4 Y	Poor	+	+
8	M/30	2 Y, 9 M	7 D*	Good	0	0
9	M/50	2 Y	2 Y	Good	+	+
10	M/50	3 M	3 M	Good	+	+
11	F/32	18 M	18 M	Good	+	0
12	F/38	1 M	1 M	Good	0	+
13	M/31	5 Y	3 M	Poor	0	+
14	F/29	5 Y	1 Y	Good	0	0

* Y = years, M = months, D = days

midoscopic improvement was observed. Then increasing amounts of a high caloric, high protein and low residue diet of the ordinary type were ingested and the hydrolysate-dextromaltose solution was correspondingly reduced.

Other abnormalities, such as hypochloremia, acid-base imbalance and dehydration, if present, were corrected as promptly as possible. Anemic patients received transfusions of whole blood. Emotional disturbances were given special attention, the psychiatrists being called in when their services seemed to be indicated.

Description of Patients. The fourteen cases represent thirteen patients, one of whom had a relapse. They were fairly representative of the types of disease usually encountered. (Tables I, II, III and IV.) Some cases were acute and others chronic but all were regarded as being severe. Seven of the patients had varying degrees of fever, ranging from a low grade pyrexia to the more severe forms such as occur in the fulminating types of the disease. One patient (Case XIII) had erythema nodosum and acute arthritis; another (Case XII) was three and one-

TABLE II
PROCTOSIGMOIDOSCOPIC FINDINGS AND EXTENT
OF INVOLVEMENT AS DETERMINED
ROENTGENOLOGICALLY

Case No.	Sigmoidoscopic Findings			Part of Intestinal Tract Involved According to Roentgen Examination
	Hyperemia	Edema	Ulcers	
1	Patient too ill; not examined			Entire colon and terminal ileum
2	+	0	+	Entire colon
3	+	+	0	Sigmoid
4	+	0	0	Entire colon
5	+	+	+	Descending colon and sigmoid
6	+	+	+	Entire colon and terminal ileum
7	+	+	0	Descending colon and sigmoid
8	+	+	0	Entire colon
9	+	+	0	Entire colon
10	+	0	0	Cecum and sigmoid
11	+	+	0	Entire colon and terminal ileum
12	+	+	0	Sigmoid
13	+	+	0	Entire colon and terminal ileum
14	+	+	0	Entire colon

TABLE III
CHANGES IN BODY WEIGHT IN POUNDS

Case No.	Before Onset of Illness	At Onset of Treatment	On Discharge from Hospital	On Recent Follow-up
1	90	58	78	107
2	180	150	159	162
3	152	143	143	152
4	105	80	85	109
5	164	147	150	158
6	136	106	104	118
7	175	141	145	151
8	162	152	153	165
9	136	116	120	136
10	200	181	185	187
11	138	108	104	112
12	137	124	124	122
13	121	115	109	116
14	167	152	Still in hospital	

minimum of 6 to an average maximum of 11.1 per twenty-four hours.

The duration of strict hydrolysate-dextromaltose therapy alone averaged 24.4 (seven to sixty days. The patients were hospitalized an average of 32.7 (11 to 70) days after beginning

subjected to severe emotional insults. The fever subsided when a bad domestic situation was corrected and has not returned.

Anorexia. After seven to fourteen days of therapy anorexia was replaced by appetite and subsequently by hunger. A

TABLE IV
CHARACTERISTICS OF STOOLS PRIOR TO THERAPY AND ON DISCHARGE FROM HOSPITAL

Case No.	Prior to Therapy			On Discharge from Hospital		
	No. of Stools per 24 Hours	Character		No. of Stools per 24 Hours	Character	
		Consistency	Blood		Consistency	Blood
1	8-12	L*	+	+	7-8	SF
2	6-32	L	+	+	1-2	F*
3	1-2	SF*	+	+	1	F
4	3-5	SF	0	+	1-2	F
5	6-8	L	+	+	2-4	F
6	6-7	L	+	+	0-1	F
7	10-15	L	+	+	1-2	F
8	5-6	L	+	+	5-6	L
9	10-12	L	0	+	1-2	F
10	3-4	L	+	+	0-1	F
11	6-8	L	0	+	1-2	F
12	8-30	L	+	+	1-2	F
13	4-5	L	+	+	1-2	F
14	8-10	L	+	+	1-2†	SF

* L = liquid; SF = semi-formed; F = formed

† Still in hospital

the special form of therapy. (Table V.) The private patients in the series (Cases II, VIII, IX and XII) were not kept in the hospital as long as was desirable because of the expense of hospitalization. One of them (Case VIII) continued the hydrolysate therapy at home.

RESULTS

General. Within seven to fourteen days of the institution of the therapy, an improvement in the general condition of the patient usually occurred. This was reflected in his subjective feeling as well as in his appearance and in a return of appetite.

Fever. Fever subsided without the use of sulfonamides or antibiotics in six of the seven patients. In one instance (Case I) sulfasuxidine was administered and appeared to abolish the pyrexia. In another (Case X) the fever relapsed when the patient was

complaint of hunger was the most reliable sign heralding the patient's subsequent improvement. Stigmas of vitamin deficiency (cheilosis and glossitis) present on admission in two patients (Cases I and II) disappeared.

Body Weight. During the period of liquid alimentation most of the patients maintained or gained weight. Some of this was due to retained fluid since loss of weight and diuresis usually occurred when the transition to an ordinary diet was first made. Maximal weight gain was not attained until a high caloric and low residue, but otherwise normally mixed diet, was ingested, especially after the resumption of home-cooked food. The average gain in weight was 3 pounds (-6 to 20) at the time of discharge from the hospital, and at the time of the latest follow-up, 13.4 pounds (-2 to 49). (Table III.)

Stools. When the liquid dietary regimen was instituted, the number of stools per day promptly decreased, remained the same or, in a few instances, increased. A sharp increase in the number of rectal discharges indicated that either some situation had arisen which had upset the patient

proctosigmoidoscopic appearance was that of hyperemia, edema and, on passage of the scope or light wiping, a tendency to bleed. (Table II.) Actual ulcerations usually were not seen until the edema had subsided, at which time they were seen in all patients examined.

TABLE V
DURATION OF THERAPY

Case No.	No. of Days Hydrolysate and Dextrimaltose Were Only Source of Calories	Total No. of Days in Hospital
1	31	41
2	20	21
3	7	11
4	19	37
5	56	70
6	30	40
7	23	25
8	7	13
9	10	14
10	28	40
11	14	23
12	16	21
13	60	70
14	30	Still in hospital

emotionally, that the concentration of the solution was excessively hypertonic or that the solution had become contaminated with bacteria. Respite from the emotional upset or correction of the abnormality in the diet consistently resulted in a reduction in the amount of diarrhea.

The most consistent and striking decrease in the number of stools occurred when the patient was again placed on an ordinary high caloric, low residue and bland diet. The stools also became formed. At the time of discharge from the hospital (Table IV) the number of stools varied from an average minimum of 1.6 to an average maximum of 2.6 per twenty-four hours. The two patients (Cases I and VIII) who had five to eight stools per day at the time of discharge from the hospital were permitted to leave before complete remission was induced. A decrease in the number of stools occurred subsequently as they continued to improve.

Proctosigmoidoscopic Appearance. Prior to the onset of therapy the most frequent

TABLE VI
FOLLOW-UP DATA

Case No.	Duration of Remission (mo.)	Weight Gain Since Discharge from Hospital (lbs.)	No. of Stools per 24 Hours	Ability to Resume Pre-illness Status
1	17+	29	2-3	+
2	9*	3	1-2	+
3	15+	9	1	+
4	13+	24	1	+
5	8+	8	2-3	+
6	8+	14	1-2	+
7	8+	6	2-3	+
8	6+	12	3-4	+
9	5+	16	1-2	+
10	4+	2	0-1	+
11	4+	8	2-3	+
12	2½+	-2	1-2	+
13	1+	7	3-4	Convalescing
14			Still in hospital	

* Relapsed; data refer to status immediately prior to relapse.

The improvement in the proctoscopic appearance was the form of objective evidence that appeared to parallel the clinical course of the patient most closely. At the time of discharge from the hospital the status of the involved lower bowel was reported as "healed" in one case (Case III), "no change" in one (Case VIII) and "improved" in ten. One patient (Case I) was not proctoscoped because of marked apprehension. Five of the ten patients who were considered improved at the time of discharge have been reported as healed at subsequent examination. It has not been possible to examine proctoscopically the remainder, but clinically they are now in remission.

Roentgen Appearance of the Colon. Improvement in the roentgen appearance of the colon usually lagged behind that observed

clinically and sigmoidoscopically. In only one of the patients (Case XII) was the colon reported to be normal at the time of discharge from the hospital. In the remainder the appearance by barium enema was reported as no change or improved. Follow-up barium enema studies were per-

TABLE VII
COMPARISON OF CLINICAL CHARACTERISTICS AND DURATION
OF THERAPY IN INTUBATED AND NON-INTUBATED
PATIENTS

	Intubated	Not Intubated
No. of cases.....	12	14
Age in years.....	11 to 58	13 to 60
Duration of disease.....	1 M to 15 Y	1 M to 16 Y
Duration of attack treated.....	26 D to 9 M	7 D to 4 Y
Apparent psychogenic motivation.....	11	14
No. with fever.....	8	7
No. with fulminating type.....	4	1
No. of stools per 24 hours.....	2 to 25 (7.7 to 13.8)*	1 to 32 (6 to 11.1)*
Loss of weight.....	31* (10 to 98)	20* (6 to 34)
Terminal ileum involved in.....	3	4
Duration of liquid diet in days.....	26.1* (5 to 52)	24.4* (7 to 60)
No. of days in hospital.....	52.5* (5 to 126)	32.7* (11 to 70)

* Average

formed when possible. These revealed either progressive improvement or no detectable change.

Relapses and Follow-ups. (Table VI). A satisfactory remission was induced in all of the fourteen patients. A relapse occurred in one. (Case II.) It occurred when he learned that he was to be transferred to another section of the country shortly after he had purchased and moved into a new home. The relapse occurred after nine months of freedom from symptoms of colitis and of useful employment. A remission has again been induced. (Case VIII.)

Intubation. The clinical, sigmoidoscopic and roentgen characteristics of the group of twelve patients (Tables VII, VIII and IX) that were subjected to intubation were

comparable to those of the group that were treated without intubation, with certain exceptions. The intubated group had lost more weight (an average of 11 pounds) and, in contrast to one such patient in the latter group, included four patients with the severe fulminating type of the disease.

TABLE VIII
COMPARISON OF RESULTS IN INTUBATED AND
NON-INTUBATED PATIENTS AT DISCHARGE
FROM HOSPITAL

	Intubated (12 cases)	Not Intubated (14 cases)
Satisfactory clinical remission.....	11	14
Deaths.....	1	0
No. of stools per 24 hours.....	0 to 6 (1.7 to 2.8)*	0 to 8 (1.6 to 2.6)*
Weight gain.....	8.2* (0 to 16)	3* (-6 to 20)
Sigmoidoscopic opinion	{ healed..... improved..... no change..... no involvement..... not examined.....	{ 1 10 1 0 2

* Average

TABLE IX
COMPARISON OF RESULTS IN INTUBATED AND
NON-INTUBATED PATIENTS ON MOST RECENT
FOLLOW-UP

	Intubated (12 cases)	Not Intubated (14 cases)
Relapses.....	3 (7, 9, and 13 M)	1 (9 M)
Duration of remission in non- relapsed patients.....	15.6 M* (5 to 23 M)	8.2 M* (1 to 17 M)
No. able to resume pre-illness duties.....	11	12†
No. of stools per 24 hours.....	0 to 6 (1.2 to 3)*	0 to 4 (1.5 to 2.2)*
Weight gain.....	16* (0 to 34)	13.4* (-2 to 49)
Sigmoidoscopic opinion	{ healed..... improved..... no involvement..... not examined.....	{ 6 2 0 6

* Average

† Two patients still convalescing; one at home and the other in the hospital

The period during which the liquid diet was administered was similar in the two groups although the intubated group spent more time in the hospital. One of the reasons for this was the fact that four of the patients in the non-intubated group were private patients and, because of the expense, were hospitalized for a shorter time.

The follow-up results are quite comparable in the two groups. Three in the intu-

bated group have had relapses as compared to one in the other group, but the follow-up period for them was seven months longer. More of the non-intubated patients may relapse as time goes on. At present all of the patients in both groups are clinically well. Only two, and they of the more recently treated patients in the non-intubated group, have not as yet resumed their pre-illness employment status; one is convalescing at home and the other has not left the hospital.

COMMENT

The foods of the usual diet are not satisfactory in the management of idiopathic ulcerative colitis during the stage of acute inflammation for various reasons: The average patient has already become malnourished with such a diet available to him and is in negative nitrogen balance. Even if consumed in adequate amounts, Elsom, Dickey and Chornock² have shown by study of the nitrogen content of the ileal discharges in four of seven severely ill patients, the protein fraction of the usual diet is poorly absorbed. That portion we now know is essential for the repair of damaged tissue such as occurs extensively in this disease. Also, on the basis of physiologic experiments, it is clear that the residue of the ordinary diet as it passes into the colon induces active peristalsis, even mass movements.

On the other hand, the casein hydrolysate-dextrimaltose solution seems advantageous for nutrition of the colitis patient for the following reasons: (1) It permits a large protein and calory intake; (2) it supplies the protein in a readily absorbable form (Emery and McGee);³ (3) it tends to convert a negative into a positive nitrogen balance; (4) it has little if any residue, thus preventing undue irritation of the diseased colon.

Certain practical difficulties, however, are encountered in using such alimentation as the sole source of calories. The patient must be willing to subsist on the solution and continue its ingestion until objective

evidence of healing occurs. Some dislike it at first because of its unpalatable taste; however, the average patient becomes accustomed to it in about two days. At times, particularly at the onset of therapy, it may be necessary to adjust the concentration of the solution. If too concentrated, it remains in the stomach until diluted sufficiently by gastric juice. Under such conditions subsequent feedings, administered at two-hour intervals, may be retained until gastric fullness, nausea and vomiting occur. When this happens, the patient is instructed to omit the next feeding until sensations of nausea and gastric fullness have disappeared and to follow the subsequent feedings with a glass of water to shorten the period of retention in the stomach. The next day the solution is made up and administered in less concentrated form. The solution itself may give rise to diarrhea if it finds its way into the intestine in hypertonic form or if it becomes contaminated with bacteria. This latter occurrence can be detected by the loss of its clear appearance. However, if the milk bottles are sterilized and when filled are put in the refrigerator, this does not occur. It is important to use a hydrolysate preparation which dissolves completely. If it fails to do so, it should not be used. The patients are permitted water as desired as well as hard candy to get rid of the taste of the solution.

Included in management of the patients is an attempt to discover and successfully to handle the emotional problems which appear to be important in the motivation of the disease. All of our patients (with the possible exception of one who was allergic to dairy products) were tense, high strung, exacting, apprehensive and hyperreactors to emotional disturbances. In some instances the rapidity of response appeared to be directly proportional to our success in helping the patient readjust himself to a bad situation. Following discharge from the hospital, the patients are followed when possible at regular and frequent intervals and are encouraged to return for observation at any time when threatening situations

arise. In a number of instances it is believed that relapses were thus aborted. The patient as well as the disease must be treated.

In view of our satisfactory results with the hyperalimentation regimen of therapy in non-intubated patients it is planned to reserve medical ileostomy for special patients, such as those with excessive small intestinal hypermotility, those with threatened perforation, those with tenesmus from an inflamed and irritated rectum and those in whom the diarrhea does not subside when the hyperalimentation method alone is employed.

SUMMARY

The results obtained in the treatment of fourteen cases (thirteen patients) of chronic idiopathic ulcerative colitis by a plan of hyperalimentation are presented. The method permits ingestion of a large number of calories and a large amount of protein in readily assimilable form and with little residue. This is accomplished by oral administration of a solution of equal parts of an enzymatic casein digest and of dextrimaltose. After varying periods of time the amount of the solution is reduced and gradually increasing amounts of substantial foods, low in residue, are ingested. Essential vitamins and iron are added.

Objective evidence of improvement con-

sists of cessation of fever, disappearance of anorexia and of the stigmas of vitamin deficiency, return to normal in the number and character of the stools and gain in weight and in sigmoidoscopic evidence of improvement in the diseased portion of the bowel.

A satisfactory remission was induced in all of the fourteen patients treated. A relapse occurred in one patient after nine months of freedom from the symptoms of colitis.

The results are compared with those obtained in patients who were subjected for a temporary period to a medical ileostomy. Except for minor differences, the end results are quite similar.

The use of medical ileostomy has not been abandoned but is reserved for special cases since the regimen just described seems to be effective in most uncomplicated cases.

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Chronic Gastritis*

A Study of Symptoms and Gastric Secretion

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ALARGE literature concerning chronic gastritis has accumulated since the appearance in 1937 of Schindler's valuable book on gastroscopy. The role of gastritis in the production of symptoms, however, remains a controversial topic. Schindler has wisely stated, "The surest approach to the problem of symptoms would be the statistical approach."¹ Using such a method we have endeavored to answer the following questions: (1) Does chronic gastritis cause symptoms? (2) If so, do the three commonly recognized types of gastritis (atrophic, superficial and hypertrophic) produce specific symptoms? (3) What is the pattern of hydrochloric acid secretion following the injection of histamine in persons with chronic gastritis as compared with individuals with normal mucosae?

METHODS AND RESULTS

Symptoms. Four groups of patients were studied: (1) Fifty patients with atrophy of the gastric mucosa; (2) fifty with superficial gastritis; (3) fifty with hypertrophic gastritis and (4) a control group of one hundred individuals whose gastric mucosae appeared normal. All patients underwent gastroscopy because of digestive complaints. The absence of other organic disease was established insofar as possible by the clinical history, physical examination, blood counts, urinalyses, blood serologic tests and x-rays of the upper gastrointestinal tract in all of the 250 patients. Barium enemas were performed in 218 and cholecystograms in 137; all were normal. Proctoscopic examinations

and benzidine tests for occult blood in the stools were carried out in nearly all patients and were essentially negative. The patients were selected simply on the basis of unequivocal gastroscopic findings and adequate diagnostic investigation. Among those with gastritis the *minimum* requisites for inclusion in the study were either moderate to marked changes involving at least one-third of the stomach or mild, extensive gastritis. The only symptoms considered were those elicited before gastroscopy so that none were brought out in the light of the gastroscopic findings.

The results of the symptomatic survey are tabulated in Table I. Pain and distress were partially separated. Distress was taken to signify any abdominal discomfort other than pain. Arbitrarily, if "distress" was an important or the only complaint, it was tabulated but if it was mentioned merely as a mild accompaniment of pain, the pain was listed without the addition of "distress." In a few instances both were prominent enough to warrant recording.

It will be noted that "weakness" has been listed. This is a difficult symptom to evaluate but was included because it has been attributed to atrophy of the gastric mucosa.²

The symptoms apparently did not vary significantly among the four groups. Three per cent of the control group and 4 per cent of those with superficial gastritis had no pain or distress while 14 and 18 per cent of those with hypertrophic gastritis and atrophy, respectively, had none. Abdominal pain, the most frequent complaint, showed little difference in incidence, occurring in 64 per cent of those with atrophy and hypertrophic

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gastritis, in 78 per cent of the superficial gastritis group and in 79 per cent of the controls; it was present in the epigastrium (the most common location) in from 44 per cent of the patients with atrophy to 72 per cent of the controls. Generalized abdominal pain occurred in 24 per cent of the group with atrophy and in 11 to 12 per cent of the

others. Burning pain was described most frequently by the control subjects; cramp-like pain was most common among the individuals with atrophy, but the differences are not striking. Antacids, milk and food were slightly less effective in the relief of pain in persons with atrophy than in members of the other three groups. The time of

TABLE I
SYMPTOMS ENCOUNTERED; EXCEPT FOR THE TWO TOP ROWS THE FIGURES REPRESENT PERCENTAGES

	Atrophic	Superficial	Hypertrophic	Normal
No. of patients.....	50	50	50	100
Average age.....	52	44	42	42
No pain or distress.....	18	4	14	3
Pain.....	64	78	64	79
Distress.....	20	20	22	28
Location:				
Epigastrium.....	44	68	62	72
Generalized.....	24	12	12	11
Low.....	8	2	10	5
Back.....	6	6	8	9
Type:				
Fullness.....	22	26	28	25
Burning.....	14	18	14	28
Gnawing.....	4	6	6	9
Sharp.....	8	10	2	5
Dull.....	6	16	20	19
Cramp-like.....	16	8	4	7
Soreness.....	4	4	4	8
Not described.....	12	8	16	10
Relieved by:				
Antacids.....	12	24	24	24
Milk.....	4	8	8	9
Food.....	12	18	24	18
Belching.....	12	16	12	9
Vomiting.....	4	2	0	2
Defecation and/or flatus.....	16	20	16	11
Heat.....	2	4	4	1
Rest.....	4	4	4	3
Time of occurrence				
Immediately after meals.....	20	12	16	20
An interval after meals.....	34	40	50	36
Awakening at night.....	14	12	14	8
Constant.....	12	16	16	9
No pattern.....	16	16	8	26
Nausea.....	32	24	24	32
Vomiting.....	12	10	14	14
Hematemesis.....	0	2	6	0
Anorexia.....	22	18	16	14
Constipation.....	32	26	20	33
Diarrhea.....	22	4	10	12
Melena.....	4	6	6	1
Weight loss.....	30	40	26	32
Weakness.....	20	18	12	14
Insomnia.....	4	0	0	3
Bad taste.....	4	2	2	2
Sore tongue.....	4	2	2	1
Numbness or tingling.....	6	2	0	1

occurrence was remarkably constant among the four groups. The discomfort was noted following a distress-free interval of twenty minutes to four hours after meals in 50 per cent of the hypertrophic gastritis group, 40 per cent of those with superficial gastritis,

exclude patients with other organic disease none was included who had persistently positive benzidine tests for occult blood in the stools.

Secretion. It was possible to determine quantitatively the gastric secretory response

TABLE II
ACID SECRETION; FASTING SPECIMENS ARE NOT INCLUDED

	Atrophic	Superficial	Hypertrophic	Controls
No. of patients	33	26	29	77
Average total mg. HCl	122	295	369	349
Average total volumes	96	137	152	136
Average units free HCl	23	49	60	66

36 per cent of the normals and 34 per cent of patients with atrophy. Distress immediately after eating was noted in 12 to 20 per cent of all the subjects; in 9 to 16 per cent the pain or distress was said to be constant; 8 to 14 per cent were awakened at night. No particular pattern was described by 8 per cent of patients with hypertrophic gastritis, 16 per cent of those with superficial gastritis or atrophy and 26 per cent of the controls.

Diarrhea occurred in 22 per cent of patients with atrophy as compared with 4 to 12 per cent of the other groups. Numbness or tingling of the extremities was reported by 6 per cent of patients with atrophy of the gastric mucosa and in 0 to 2 per cent of the remaining subjects. There were essentially no differences in the incidences of nausea, vomiting, anorexia, constipation, weight loss, weakness, bad taste or sore tongue. This was also true of the duration of symptoms and the degree of weight loss.

A history of hematemesis was given by 6 per cent of patients with hypertrophic gastritis, 2 per cent with superficial gastritis and by none of the remaining groups. Melena was described by 4 to 6 per cent of patients with gastritis and by one of the controls. However, the figures on bleeding may be misleading for, in order to eliminate from the study persons with weakness due to anemia, all who had red blood counts below 4 million or hemoglobin values below 12 Gm. were excluded. Furthermore, to

to histamine in 165 patients, measuring the total mg. of free hydrochloric acid, total volume and average units of free acid, as indicated in Table II. There was little average difference in total acid secretion between individuals with hypertrophic gastritis and the control subjects during the hour after subcutaneous injection of histamine. The average total mg. and the average total volumes were slightly higher in the hypertrophic gastritis patients but the average units of free acid were higher in the normals and none of these differences appears clinically significant. Although the average volume of secretion in the patients with superficial gastritis fell within the range of the hypertrophic gastritis group and the controls, the average acid output was less even though two of this group secreted very large amounts of acid. (Fig. 1.) Patients with atrophy of the gastric mucosa secreted the smallest amounts of acid. The range of acid output was found to be very wide, the highest secretor being a patient with superficial gastritis who produced 1,277 mg.

When the differences among the means of total mg. of acid secreted were evaluated from a statistical point of view, highly significant differences were found between the group with atrophy and the controls, and between the groups with atrophy and hypertrophic gastritis. The difference in total mg. between the superficial gastritis and atrophy groups also is significant. A

statistical analysis of the differences between the means of total volumes and clinical units of free hydrochloric acid also indicated significant differences when the same comparisons were made. Other differences could not be proved to be significant.

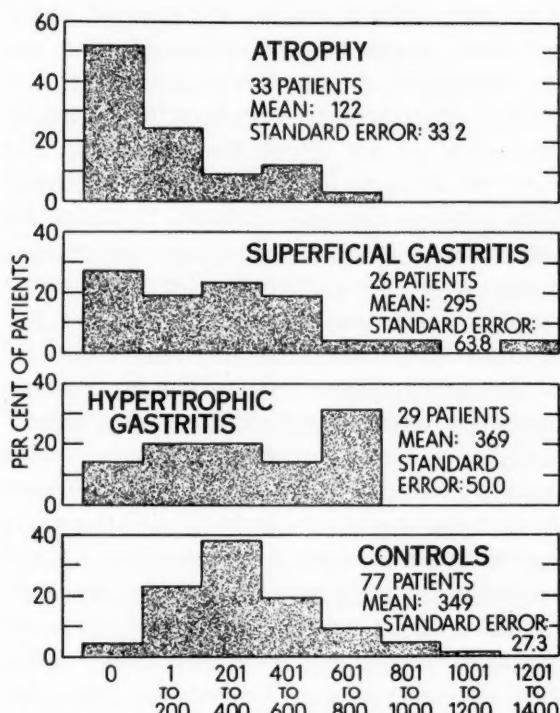


FIG. 1. Distribution of total mg. of hydrochloric acid secreted during one hour after injection of histamine.

The distribution of patients secreting a total of more than 600 mg. of acid in response to histamine was compared by use of an exact formula for calculating probabilities, employing a four-fold table.³ The proportion of individuals with hypertrophic gastritis who secreted more than 600 mg. was significantly greater than that of persons with normal mucosae or with atrophy. The present data indicate that similar hypersecretion occurs more commonly in normals than in persons with atrophy, and more often in those with hypertrophic gastritis than in persons with superficial gastritis. However, the probability that this distribution could occur entirely due to chance errors was found to be approximately 0.06 when assayed by this method. This figure is slightly greater than the usually accepted upper limit of statistical significance, 0.05.

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No significant difference could be proved to exist in this regard between the control and superficial gastritis groups nor between the atrophic and superficial gastritis groups.

The incidence of anacidity after histamine (Fig. 2) was 52 per cent of thirty-three

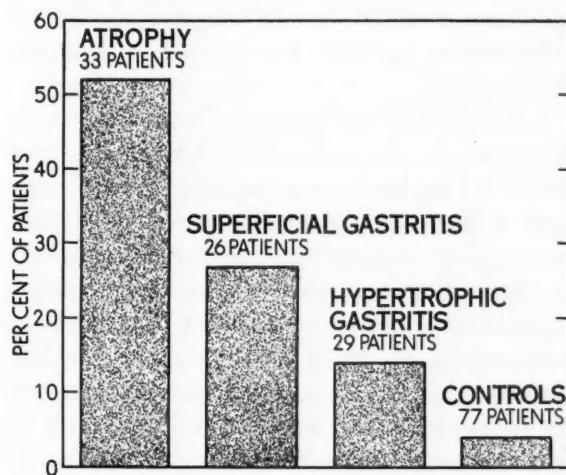


FIG. 2. Incidence of histamine anacidity.

patients with atrophy of the gastric mucosa, 27 per cent of twenty-six with superficial gastritis, 14 per cent of twenty-nine with hypertrophic gastritis and 4 per cent of seventy-seven controls. In this series the differential incidence between patients with atrophy and controls and between individuals with superficial gastritis and the same control group was found to be statistically highly significant. However, in the comparison between the hypertrophic gastritis group and the controls chance alone could have accounted for the distribution 7.1 times in one hundred, as estimated by use of the aforementioned four-fold table.

COMMENTS

Symptoms.—The answers which these data offer to the questions posed in the introductory paragraph are for the most part not categorical. Since all patients had complaints that led to gastroscopic examinations, they do not represent a cross section of the general population and the control group is not truly a "normal" group. Indeed, unless this is kept in mind it might at first seem unusual that such a high percentage of the patients with normal mucosae had epi-

gastric pain. The greatest variations from group to group occurred in the incidences of epigastric pain (44 per cent among patients with atrophy to 72 per cent among the normals) and of diarrhea (22 per cent of patients with atrophy compared with 4 to 12 per cent for the other groups). These differences appear to be of uncertain significance.

The incidence of gastritis in patients with dyspepsia has been found to be 42 to 44 per cent.⁴⁻⁶ The incidence in patients of similar ages without symptoms is not known precisely. The beginning of a series designed to explore this problem was reported by Fitzgibbon and Long⁷ who found that thirty-eight of forty healthy young adult males had a normal-appearing mucosa; the remaining two had hypertrophic gastritis. A similar investigation consisted in the gastroscopic examination of thirty-three volunteers with an average age of twenty-five years.⁸ All were normal except three who had mild, patchy atrophy of the gastric mucosa. Ruffin and Brown examined thirty-two students having no complaints and found normal mucosae in all instances except five, in which only hemorrhagic or pigment spots were seen.⁹ Thus, chronic gastritis was observed in only 5 of 102 young asymptomatic volunteers.

Two groups of young subjects with dyspeptic symptoms referred to the upper abdomen were studied gastroscopically during World War II. All had normal gastroduodenal x-rays. One group was composed of 110 soldiers near a battle area in Italy.¹⁰ Redness and edema of the gastric mucosa were noted in twenty-nine, unequivocal superficial gastritis in sixteen and hypertrophic gastritis in two. The preponderance of superficial changes was chiefly attributed to the unusually high degree of anxiety manifested by these patients. In the other group consisting of eighty-three soldiers in the United States only ten instances of hypertrophic gastritis, atrophy or mixed hypertrophic gastritis and patchy atrophy were found.¹¹ Although the former group was in a sense selected, and despite the fact

that gastroscopic interpretations vary, these findings appear to lend support to the thesis that abnormalities of the gastric mucosa are more common among persons with abdominal complaints than among asymptomatic persons. The more advanced ages of persons with atrophy, as exemplified by our data, suggests an explanation for the low incidence of atrophy in the soldiers.

Gray gastroscoped one hundred chronic alcoholics in an effort to determine the effect of alcohol on the gastric mucosa.¹² After noting the gastroscopic findings he interrogated them regarding symptoms. "Only 4 of 55 patients with normal or essentially normal stomachs had mild abdominal and epigastric distress, while 24 of the 45 patients with chronic gastritis presented definite subjective complaints." Symptoms were present in twelve with superficial gastritis, including two in whom the distress was ulcer-like; ten with the same type of gastritis were symptom-free. Of the patients with atrophy twelve had symptoms, including four who complained only of profound weakness; the remaining nine were asymptomatic. The two patients with hypertrophic and hyperplastic nodular gastritis did not have symptoms. No statements were made regarding the ages of these subjects, nor was there mention of x-rays, blood counts or other studies to exclude the possibility of other organic disease.

Schindler has concluded that the common types of chronic gastritis are usually characterized by distinctive symptoms.¹ The patient with superficial gastritis is considered to have one outstanding complaint: epigastric pain, usually moderate and vague but sometimes constant; nausea, anorexia, weight loss, weakness and diarrhea may occur. Atrophy of the gastric mucosa is thought to produce "an entirely different picture"; the syndrome changes if the superficially inflamed gastric mucosa becomes atrophic. Although epigastric distress is usually present, this is of secondary importance to profound weakness and fatigue, often associated with anorexia and weight loss. Paresthesias, numbness and tingling

of the extremities and soreness of the tongue are said to be frequent. Hypertrophic gastritis, on the other hand, is thought to mimic peptic ulcer frequently. Nausea, vomiting and gross hemorrhage are considered common in all three types. Similar opinions have been expressed by Carey.¹³ McClure, Sweetser and Jankelson, in contrast, concluded that the symptomatology of hypertrophic gastritis and atrophy is similar, except that excessive fatigability is more common in the latter.⁶

Gordon studied seventy-eight patients with chronic gastritis, all of whom had upper abdominal distress.¹⁴ He correlated symptoms with gastroscopic observations in two groups of patients and found that those with ulcer-like symptoms usually had hypertrophic gastritis whereas those with early graying of the hair, weakness, excessive fatigue, anorexia, vomiting and epigastric distress more often had atrophy of the gastric mucosa. It was not possible to state that the patients in the latter group did not have mild or incipient pernicious anemia. The symptoms of persons with superficial gastritis, who comprised 53 per cent of the entire group, fell into neither category. The author suggested that superficial gastritis and atrophy of the gastric mucosa are usually "incidents in the course of a neurosis, and similar to neurodermatitis in their significance."

Symptoms accompanying hypertrophic gastritis have been likened to those of peptic ulcer by others.¹⁵⁻¹⁹ The symptoms of fifty patients with superficial gastritis were analyzed by Bank and Renshaw.²⁰ Our findings are remarkably similar to theirs, the widest divergence occurring in the incidence of diarrhea: 16 per cent of their patients to 4 per cent of ours. In the studies on dyspeptic soldiers recorded by Halsted *et al.*¹⁰ the symptoms were the same in patients with gastroscopic abnormalities (chiefly superficial gastritis) as in those with normal findings. These symptomatologic data, together with the previously cited observations on alcoholics by Gray,¹² on the healthy volunteers of Fitzgibbon and Long⁷ and

Cutler and Walther⁸ and on the soldiers of Berk,¹¹ are the only analyses found in the literature which include persons with normal gastric mucosae.

Except for the inclusion of patients with normal gastroscopic findings, the present study is similar to one by Horner who recorded the symptoms of three groups of fifty patients each, representing superficial and hypertrophic gastritis and atrophy of the gastric mucosa.²¹ The results are similar in many respects, but in some there is a striking difference, the outstanding example being the incidence of epigastric pain with atrophy: none in Horner's series and 44 per cent in the present group. The occurrence of epigastric distress in the two groups is approximately the same. Epigastric pain was present in twenty-six of forty-one patients with atrophy described by Schindler and Murphy.²

Maimon and Palmer observed the changes in appearance of the gastric mucosa in fourteen patients (ten with gastric ulcer), each of whom was gastroscoped from four to one hundred times over periods of six months to eleven years.²² Normal findings and the three common types of gastritis were found, sometimes in the same patient, but it was "not . . . possible to correlate the appearance of the gastric mucosa with symptoms of any kind." This is in accord with experience previously noted by one of us (W. L. P.).²² Furthermore, the superficial gastritis and the mucosal atrophy following application of moderate doses of roentgen irradiation to the stomach are not accompanied by symptoms.²⁴

X-ray examination may fail to disclose an undetermined but presumably small number of duodenal ulcers in undeformed bulbs; rarely a small, superficial gastric ulcer may escape detection both roentgenographically and gastroscopically. This may account for a small proportion of the ulcer-like symptoms described by our patients, chiefly those with normal gastric mucosae and hypertrophic gastritis, and to a lesser degree those who secrete less acid, the superficial gastritis and gastric mucosal atrophy groups.

Secretion. Faber observed usually a low output of acid in individuals with atrophy of the gastric mucosa.²⁵ Although no evidence was submitted, it was his opinion that chronic inflammation of the stomach produces increased acid secretion. Using the Ewald test, Henning found "hyperacidity" in 11 per cent of patients with "simple" chronic gastritis, normal acidity in 21 per cent, "hypoacidity" in 32 per cent, anacidity in 21 per cent; histamine-anacidity was encountered in 15 per cent.²⁶ In a group of forty-three patients with gastritis Swalm, Jackson and Morrison observed hypo- and anacidity chiefly in those with atrophy.²⁷ Schindler and Murphy found histamine-achlorhydria in nine of thirty-six patients with atrophy of varying degrees.²

Review of three studies²⁸⁻³⁰ on a total of 294 patients with histamine anacidity in the absence of other abnormalities indicated that ninety-nine exhibited atrophy of the gastric mucosa, sixty-six had superficial gastritis, sixty-one had superficial gastritis with atrophy, fifteen demonstrated hypertrophic gastritis, two showed solitary erosions and the mucosae of the remaining fifty-one were normal.

Bank and Renshaw found among fifty patients with superficial gastritis thirteen with histamine-achlorhydria although twenty-five had what was considered to be hyperacidity (more than 50 units of free acid secreted during two hours after an Ewald test meal).²⁰ Only the remaining twelve secreted normal or diminished amounts. These authors suggested the possibility that superficial gastritis, being a precursor of more advanced forms, is sometimes accompanied by stimulation of the acid-secreting cells. When their paper was published in 1939, it was not well known that superficial gastritis is indeed often followed by atrophy.

Gill, in an effort to stimulate acid secretion both centrally and locally, injected insulin and histamine synchronously.³¹ An unstated number of persons with normal mucosae secreted 2.5 to 3.5 cc. per minute while the rate of secretion in persons with

hypertrophic gastritis was 6 to 6.5 cc. of more concentrated acid per minute. Those with gastric mucosal atrophy had anacidity and secreted a volume of less than 1 cc. per minute.

The present findings demonstrate that patients with atrophy of the gastric mucosa produce a low average acid output in response to histamine; the average acid secretion is significantly lower and the incidence of achlorhydria is significantly higher than in persons with other types of gastritis or with normal mucosae. The occurrence of hypersecretion (arbitrarily, more than 600 mg. of free acid during an hour after histamine injection) is less frequent in atrophy than in hypertrophic gastritis or controls.

Diminished acid secretion often occurs in superficial gastritis, as evidenced by the findings of Bank and Renshaw²⁰ as well as our own. The incidence of anacidity, although significantly lower than in atrophy, is significantly higher than in normals or in persons with hypertrophic gastritis. However, that this type of inflammation is compatible with a high output is indicated by secretions of more than 600 mg. of free acid in 12 per cent of our patients and by hyperacidity in one-half of the patients of Bank and Renshaw. Superficial gastritis and subsequent atrophy often occur in individuals in whom a lowered secretion is produced by x-ray therapy directed to the gastric fundus.²⁴

The incidence of histamine anacidity in our patients with hypertrophic gastritis is lower than in the other two types of gastritis. There is a 7.1 per cent probability that the higher incidence of anacidity in hypertrophic gastritis than in normals, as found in this study, is due to chance. This figure, although slightly higher than the usually accepted level of statistical significance, when considered in conjunction with the fact that hypersecretion could also be proved to be more common in this type of gastritis than in the controls, may account for the mean total output of acid being approximately the same in the two groups.

SUMMARY

To evaluate more fully the clinical significance of chronic gastritis in patients with gastrointestinal symptoms, a comparative analysis was made of the symptomatology and of the gastric secretory response to histamine among four groups of patients: fifty patients with atrophy of the gastric mucosa, fifty with superficial gastritis, fifty with hypertrophic gastritis and one hundred individuals in whom the gastric mucosa appeared normal gastroscopically. The absence of other organic disease was established by physical examinations, blood counts, urinalyses, proctoscopies and by x-rays of the gastrointestinal tract. The symptoms, with few exceptions, showed no unequivocal variation among the four groups.

Histamine anacidity was present in 52 per cent of thirty-three patients with atrophy of the gastric mucosa, 27 per cent of twenty-six with superficial gastritis, 14 per cent of twenty-nine with hypertrophic gastritis and 4 per cent of seventy-seven controls. The differences between these incidences and the control value were, with one exception, statistically significant. A quantitative analysis of histamine tests performed in these 165 patients indicated that the smallest average acid secretion was exhibited by patients with atrophy of the gastric mucosa, with superficial gastritis next. A few patients with superficial gastritis, however, secreted large amounts of acid. The average total output of acid in patients with hypertrophic gastritis did not differ significantly from that of individuals with normal mucosae. Nevertheless, a statistically significant proportion of the hypertrophic gastritis group secreted excessive quantities of acid in response to histamine stimulation.

CONCLUSIONS

1. The common types of chronic gastritis apparently produce no symptoms; distress, when present, has no characteristic pattern.
2. Histamine-anacidity occurs most frequently in association with atrophy of the gastric mucosa. The mean secretion of acid

(histamine) is lowest in patients with mucosal atrophy.

3. Some individuals with superficial gastritis are capable of producing large amounts of acid, but the mean histamine secretion is less than it is in persons with hypertrophic gastritis or in controls. The incidence of anacidity in superficial gastritis is second only to that in atrophy.

4. The incidence of histamine anacidity seems greater in patients with hypertrophic gastritis than in persons with normal mucosae, but the mean acid secretion is approximately the same. This may be due to the fact that a certain proportion of individuals with hypertrophic gastritis secrete excessive amounts of acid.

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Review

A Unified Concept of Cardiac Failure*

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INCREASED venous and atrial pressure observed in cardiac failure has been attributed by various investigators to: (1) a damming of blood, or back pressure, (2) an increase in the blood volume or (3) a decrease in the capacity of the venous side of the circulatory system.

As a result of work with the heart-lung preparation Starling proposed that the increase in venous pressure seen in cardiac failure is due to a "back-pressure" or "damming" phenomenon. This concept has been discussed at length by Harrison.¹ Starr² observed that in patients dying of cardiac failure the venous pressure was elevated after death. He believed that the increased venous pressure during life could not be ascribed to a damming of the blood and therefore he questioned the validity of this concept. Warren and Stead³ observed an increase in body weight and in plasma volume in patients with congestive failure before there was an appreciable increase in venous pressure, and they ascribed the increase in venous pressure to an increased blood volume due to retention of salt and water. Merrill⁴ has reported salt retention in congestive failure due to a decreased glomerular filtration rate.

If it be accepted that the increased venous pressure seen in congestive failure is due to an increased blood volume, or if it be accepted that it is due to damming of the blood, then one must turn to other explanations for the increased venous pressure seen in cardiac failure due to anemia since McMichael⁵ has called attention to the report of Sharpey-Schafer that in anemic heart failure with an increased cardiac out-

put the blood volume is often low in the presence of considerable increases in venous pressure. McMichael states: "In these cases of 'anemic heart failure' the rise in venous pressure cannot be ascribed to failure of the heart to keep on pumping blood through the body at an adequate rate, as the output is usually more than double the normal value. The pulse pressure is increased, indicating that the arterioles are dilated (the output being high and the mean arterial pressure somewhat reduced). Since the volume of blood in circulation (often below 3 liters) must be equal to the capacity of the total vascular bed, the latter must be markedly reduced. This reduction does not take place on the arterial side; as the larger veins are full and often distended, it must take place in the capillaries and venules. It is on such clinical evidence that we find it necessary to postulate an active venomotor mechanism for maintaining and even raising the venous pressure to the required level."

UNIFIED CONCEPT OF CARDIAC FAILURE

At the present time there is no single unified concept of cardiac failure which will explain the increase in atrial pressure seen in all types of cardiac failure. Evidence is presented in this paper which supports the view that the increase in blood volume will not account adequately for the increase in atrial pressure seen in congestive heart failure. Evidence is also presented which supports the hypothesis that a decrease in the mixed venous pO_2 (partial pressure of oxygen) probably serves as a stimulus which results in an increased cardiac output and a decreased venous capacity in the normal

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individual, the decreased venous capacity being due to venoconstriction. The mechanism for these effects may be by means of reflexes or by means of humoral control, or both. Normally with an increased oxygen demand, such as in exercise, there would be

statistical analysis.⁷ In some instances new data have been derived by calculation from published observations.

Relationship between Blood Volume and Atrial or Venous Pressure. If the increased venous pressure in congestive failure were due to an

TABLE I
CORRELATION BETWEEN VENOUS PRESSURE AND BLOOD VOLUME IN CONGESTIVE HEART FAILURE

Comparison	Reference	No. of Pairs of Observations	Mean		r	t	P (%)
			Venous Pressure (mm. H ₂ O)	Blood Vol. (cc.)			
Venous pressure versus blood volume	(8)	19	205	6083	0.149	0.620	> 50
Venous pressure versus blood volume	(9)	21	168	6183	0.379	1.698	> 5
Venous pressure versus excess blood volume ^x	(9)	20	171	1617x	0.529	2.687	< 5
Maximum decrease in venous pressure versus corresponding decrease in blood volume ^{xx}	(9)	15	106xx	1217	0.093	0.314	> 50

x—excess blood volume = determined blood volume—predicted blood volume.

xx—maximum decrease in venous pressure with treatment = maximum venous pressure—lowest venous pressure. The difference in the values for the determined corresponding blood volumes was used for comparison.

r = correlation coefficient.

t = "Students" t value for significance.

P = The probability of chance occurrence of the correlation.

only a slight or moderate rise in the central venous or atrial pressure, depending upon the adequacy of the increased cardiac output in response to the decreased mixed venous pO₂. Theoretically if the cardiac response were entirely adequate, there would be no increase in central venous pressure in spite of the decreased venous capacity.

In cardiac failure, whether it be acute failure, low output failure or high output failure, the cardiac response to the decreased mixed venous pO₂ would be inadequate due either to disease or to a relatively excessive oxygen demand, or to a combination of the two; and the venoconstriction resulting from the decreased mixed venous pO₂ would cause a considerable increase in central venous or atrial pressure.

ANALYSIS OF PRESENT CONCEPTS

The data presented herein were taken from the literature and subjected to sta-

increased blood volume, there should be a good statistical correlation between these two sets of data in the same patient. In Table I the correlation coefficient between the venous pressure and the blood volume in congestive failure has been calculated as well as the probability of chance occurrence of this correlation. It will be seen that there is no significant correlation between venous pressure and blood volume in these patients. Gibson and Evans⁹ estimated the excess blood volume in their patients and a significant correlation between the estimated excess blood volume and the venous pressure was found. With treatment these patients showed a decrease in venous pressure and blood volume. However, the correlation between the maximum decrease in venous pressure and the corresponding blood volume change was found to be insignificant.

The relation between venous pressure and per cent deviation from the predicted

normal blood volume while under treatment in five of Gibson's and Evans' patients will be found in Figure 1. It will be seen that at first there was considerable decrease in venous pressure which was accompanied by little or no decrease in the excess blood volume. Later there was a slight decrease in venous pressure accompanied by a considerable decrease in the excess blood volume. It will be seen also that in the patients illustrated the venous pressure value at the beginning of treatment was not related to the percentage of blood volume in excess of the estimated normal.

Although these data do not exclude the possibility that an excess blood volume contributes to the elevation of venous pressure in congestive heart failure, they do indicate that there is some other factor or factors concerned in the elevation of venous pressure in this condition. In anemic heart failure the elevation of venous pressure cannot be ascribed to an excess blood volume for the blood volume is usually either normal or diminished in this condition.⁶

Relationship between Cardiac Index and Atrial or Central Venous Pressure. In Table II it will be seen that in two groups of patients with congestive heart failure there were significant negative correlation and regression coefficients when the cardiac index and atrial or central venous pressures were compared. Of course, a significant correlation *per se* gives no information regarding causative factors in a relationship. These data could be interpreted (1) as meaning that an elevation of atrial or venous pressure causes a decreased cardiac output, (2) that a decreased cardiac index causes an elevated venous pressure in congestive failure or (3) that a decreased cardiac index affects some other function or mechanism which in turn is responsible for the elevation of venous pressure in congestive heart failure.

Considering the first possibility this interpretation of the data would fit the widely accepted concept of the operation of Star-

ling's law in congestive failure.⁶ However, this interpretation contributes no information as to the cause of the elevated venous pressure in congestive heart failure.

Considering the second possibility one might say that this interpretation favors the damming or back-pressure theory of the elevation of venous pressure in congestive

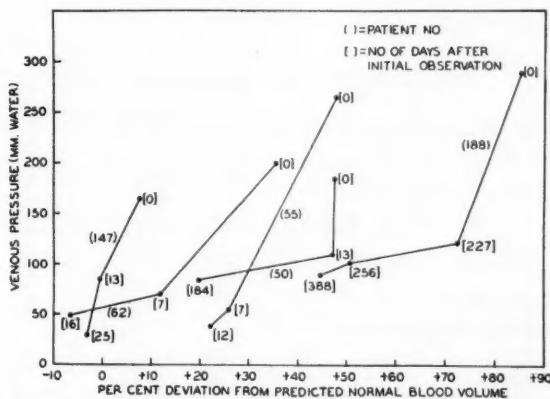


FIG. 1. Relationship between venous pressure and the excess blood volume during treatment in patients with congestive heart failure. Data taken from Gibson and Evans.⁹

failure.¹ However, it has been shown^{5,15} that when the "competency" of the dog's heart was decreased there was no significant increase in the resting venous pressure. Therefore, there may be considerable doubt that the damming or back-pressure theory of the elevation of venous pressure in congestive failure is true. Of course, this theory cannot explain the elevated venous pressure seen in anemic heart failure for the cardiac index is increased in this condition.

Considering the third possibility this is the interpretation proposed by those who favor elevation in blood volume as the causative factor in elevation in venous pressure in congestive failure.^{3,4} However, a decrease in cardiac index would probably mean that the supply to the tissues of various substances, including oxygen, would be diminished and this may cause an alteration in some mechanism, other than a change in blood volume, which would affect the venous pressure.

FURTHER RELATIONSHIPS IN CARDIAC FAILURE

Relationship between Oxygen Supply to the Tissues and Oxygen Consumption in Normal Subjects and in Patients with Cardiac or Respiratory Disease. As an expression of the adequacy with which the heart meets the tissue demands for oxygen the ratio of oxygen supply to the tissues per square

in Table III. It will be seen that significant differences between mean values for O.I. occur in the following: normal at rest and congestive failure at rest, normal with exercise and congestive failure with exercise, normal with exercise and mitral stenosis with exercise, normal at rest and normal with exercise and congestive failure

TABLE II
CORRELATION AND REGRESSION COEFFICIENTS FOR VARIOUS MEASUREMENTS IN PATIENTS
WITH CONGESTIVE HEART FAILURE

A	V.P. on C.I.	A.P. on C.I.	A.P. on C.I.	A-VO ₂ on C.I.	A.P. on AO ₂	A.P. on VO ₂	A.P. on A-VO ₂	A.P. on A-VO ₂	V.P. on A-VO ₂	A.P. on ApO ₂	A.P. on VpO ₂
B											
Reference.....	(4)	(4)	(10)	(4)	(10)	(10)	(10)	(4)	(4)	(10)	(10)
Pairs of observations.....	13	19	47	32	47	47	47	19	12	14	14
Mean for A.....	140	142	146	6.5	146	146	146	142	144	158	158
σ for A.....	65.72	65.15	91.87	1.66	91.87	91.87	91.87	65.15	67.18	103.57	103.57
Mean for B.....	2.4	2.6	2.1	2.5	15.4	8.0	7.3	6.8	6.0	55.8	21.8
σ for B.....	0.68	0.84	0.50	0.77	2.10	2.43	1.58	1.53	1.74	12.27	5.60
Correlation coefficient (r).....	-0.69	-0.46	-0.47	-0.58	-0.14	-0.37	+0.47	+0.65	+0.73	+0.04	-0.56
t for r.....	3.105	2.110	3.525	3.820	0.955	2.616	3.525	3.510	3.358	0.139	2.341
P for r (%).....	< 1	< 5	< 1	< 1	> 5	< 5	< 1	< 1	< 1	> 50	< 5
Regression coefficient (R.C.)...	-65.57	-37.31	-89.635	-1.357	-6.309	-16.70	+29.195	+27.72	+28.31	+0.403	-10.358
t for R.C.	3.224	2.192	3.751	4.406	0.976	3.332	3.760	3.536	3.418	0.166	2.320
P for R.C. (%)....	< 1	< 5	< 1	< 1	> 5	< 1	< 1	< 1	< 1	> 50	< 5

V.P. = venous pressure in mm. water or saline.

A.P. = atrial pressure in mm. water or saline.

C.I. = cardiac index (cardiac output in 1/min./sq. M.).

A-VO₂ = arterial-venous O₂ difference in cc./100 cc.

AO₂ = arterial O₂ content in cc./100 cc.

VO₂ = mixed venous O₂ content in cc./100 cc.

ApO₂ = arterial O₂ tension in mm. Hg.

VpO₂ = mixed venous O₂ tension in mm. Hg.

σ = standard deviation of the mean.

t = "Students" t value for significance.

P = Probability of chance occurrence.

meter of body surface to the oxygen consumption per square meter has been calculated. In this oxygen index, O.I. =

$O_2 \text{ supply/sq. M.}$

$O_2 \text{ consumption/sq. M.}$, the oxygen supply was calculated from the cardiac index in l/min. and the arterial oxygen content in cc./l.* The oxygen consumption was reported^{10,13,14} and these data are presented

* Since the cardiac output occurs in both the numerator and denominator, an equivalent mathematical expression of this relationship is:

$$\text{O.I.} = \frac{\text{arterial O}_2 \text{ content in vol. \%}}{\text{A-V O}_2 \text{ difference in vol. \%}}$$

at rest and congestive failure with exercise. Non-significant differences between mean values of O.I. occurred in: normal at rest and mitral stenosis at rest, normal at rest and pulmonary emphysema at rest and normal with exercise and pulmonary emphysema with exercise.

It has been shown that in the normal subject with exercise the O.I. is significantly lower than at rest. This is interpreted as meaning that in the normal subject, with the degree of exercise used in these experiments, the heart is unable to maintain the normal O.I. and therefore the A-V oxygen

difference must increase; the mixed venous oxygen content and the mixed venous pO_2 must decrease below the normal resting value. In the blood leaving the tissues there is a relative hypoxia. The O.I. in congestive failure at rest or with exercise is significantly lower than the corresponding values in the normal subject. This means that in congestive failure, even at rest, there is a failure of the heart to supply the normal amount of oxygen to the tissues. In the patients with mitral stenosis the difference from the normal O.I. at rest is not significant while with exercise it is significant, and the O.I. is only slightly greater than in the patients with congestive failure during exercise. This indicates that in the patients with mitral stenosis it is only during exercise that a failure of oxygen supply to the tissues occurs. In patients with pulmonary emphysema there was no failure of the heart to supply the normal amount of oxygen to the tissues with or without exercise. This is shown by the fact that the O.I. was not significantly different from values in the normal subjects under the same circumstances. In four cases¹⁰ of high output failure at rest, anemia and hyperthyroidism the mean value for O.I. was 2.49 which is only slightly greater than the value in congestive failure at rest. This means that in high output failure there is a failure of the heart to supply oxygen to the tissues.

It is seen then that the common feature of congestive failure, mitral stenosis with exercise and high output cardiac failure is failure of the heart to supply oxygen to the tissues in sufficient amounts. This means that there would be a considerable hypoxia of the blood leaving the tissues under these circumstances.

Some idea of the critical value of the O.I. which is indicative of cardiac failure may be derived by subtracting 2σ from the mean normal value¹⁴ and adding 2σ to the mean value for patients with congestive failure at rest.¹⁰ (Table III.) It will be seen that the overlapping critical range is 3.18 to 3.53.

Relationship between Atrial or Central Venous Pressure and Arterial and Mixed Venous Oxygen Content, Arteriovenous Oxygen Difference and Arterial and Mixed Venous pO_2 . In Table II it will be seen that there are significant negative correlation and regression coefficients between the atrial pressure and mixed venous oxygen content and mixed venous oxygen tension (pO_2).^{*} There are significant positive correlation and regression coefficients between the atrial or venous pressure and A-V O_2 difference. The correlation and regression coefficients between the atrial pressure and the arterial oxygen content or arterial oxygen partial pressure (pO_2) were not significant.

Again these correlations give no information within themselves as to causative factors. However, if an elevation in venous pressure were causing the oxygen changes noted, one would expect to find an increase in the A-V oxygen difference whenever an elevation of venous pressure occurred. Sharpey-Schafer¹⁶ reported that in uncomplicated chronic anemia, with a normal venous pressure and a mean cardiac output of 7.6 l/min., the mean A-V oxygen difference was 3.4 cc./100 cc.; while in anemic heart failure, with an elevated venous pressure and a mean cardiac output of 9.4 l/min., the mean A-V oxygen difference was 3.1 cc./100 cc. The elevation in venous pressure was not accompanied by an increase in the A-V oxygen difference.

If the oxygen changes noted are responsible for the elevation in atrial and venous pressure in congestive heart failure, which of these changes might be the causative factor? It should be remembered that the mixed venous pO_2 is not directly related to the mixed venous oxygen content since it is dependent upon the per cent saturation of the mixed venous blood with oxygen.

Certain comparisons between normal subjects and patients with uncomplicated anemia give some information regarding the causative factor. Cournand et al.¹²

* The pO_2 was calculated from the per cent arterial saturation, the arterial O_2 content and the mixed venous oxygen content using the oxygen dissociation curve at a pH of 7.44.

reported the following mean values in fifteen normal subjects: atrial pressure, 33 mm. water; A-V oxygen difference, 4.5 vol. per cent; mixed venous pO_2 , 34 mm. Hg (calculated from the oxygen saturation of

vol. per cent; calculated* mixed venous pO_2 , 30.7 mm. Hg and mixed venous oxygen content, 5.3 vol. per cent. In the patients with uncomplicated chronic anemia the only measurements with which we are

TABLE III
COMPARISON OF OXYGEN INDEX VALUES IN NORMAL SUBJECTS AND SUBJECTS WITH DISEASE

Type of Subject	Reference	No. of Subjects	Mean Value O.I.	σ for Mean of O.I.	Difference between Mean Values	<i>t</i> for Difference	Probability of Chance Occurrence of Difference (%)
Normal at rest	(14)	20	4.79	0.805	2.55	14.119	< 1
Congestive failure at rest	(10)	48	2.24	0.644			
Normal at rest	(13)	8	4.50	0.957	1.76	4.889	< 1
Congestive failure at rest	(13)	9	2.74	0.476			
Normal at rest	(13)	8	4.50		0.92	2.120	> 5
Mitral stenosis at rest	(13)	7	3.58	0.673			
Normal at rest	(13)	8	4.50		0.64	1.293	> 5
Pulmonary emphysema at rest	(13)	5	3.86	0.688			
Normal with exercise	(13)	8	3.30	0.883	1.30	4.047	< 1
Congestive failure with exercise	(13)	9	2.00	0.376			
Normal with exercise	(13)	8	3.30		0.94	2.271	< 5
Mitral stenosis with exercise	(13)	7	2.36	0.689			
Normal with exercise	(13)	8	3.30		0.39	0.911	> 5
Pulmonary emphysema with exercise	(13)	5	2.91	0.430			
Normal at rest	(13)	8	4.50		1.20	2.609	< 5
Normal with exercise	(13)	8	3.30				
Congestive failure at rest	(13)	9	2.74		0.74	3.663	< 1
Congestive failure with exercise	(13)	9	2.00				

$$O.I. = \frac{\text{oxygen supply/sq. M.}}{\text{oxygen consumption/sq. M.}}$$

σ = standard deviation.

t = "Students" *t* value for significance.

mixed venous blood using the oxygen dissociation curve at pH 7.44). A value for the mixed venous oxygen content was not given but it may be calculated to be 12.1 vol. per cent since the mean arterial oxygen content was 16.6 vol. per cent and the mean A-V oxygen difference was 4.5 vol. per cent. Compare with these data the report of Brannon et al.¹¹ in patients with uncomplicated chronic anemia: atrial pressure, 41 mm. water; A-V oxygen difference, 3.1

concerned which were normal were the atrial pressure and the mixed venous pO_2 .

Of the three oxygen factors considered the evidence is suggestive that a decreased mixed venous pO_2 is related in a causative manner to the elevation of atrial or venous

* Only those patients were used in whom there was good agreement between the arterial O_2 content as determined and as calculated from the hemoglobin content. It was assumed that the arterial O_2 saturation was 95 per cent and the oxygen dissociation curve at pH 7.44 was used.

pressure since marked alterations in the A-V oxygen difference and mixed venous oxygen content were not associated with an elevated atrial pressure.

HYPOTHESIS

It has been shown that: (1) the increased blood volume does not adequately explain the elevated venous pressure in congestive heart failure, and an increased blood volume cannot explain the elevated venous pressure in anemic heart failure; (2) although the cardiac index is related inversely to the venous pressure in congestive heart failure, there is a reasonable doubt that this can be explained on the basis of damming or back-pressure, and this mechanism cannot explain the elevated venous pressure in anemic heart failure; (3) there is a definite relationship between cardiac failure, congestive and anemic, and the ratio of the tissue oxygen supply and tissue oxygen consumption; (4) there are significant correlations between the atrial or venous pressure in congestive heart failure and the A-V oxygen difference, the mixed venous oxygen content and the mixed venous pO_2 and (5) the evidence favors a causative relationship between the mixed venous pO_2 and the atrial or venous pressure.

On the basis of this information it is postulated that normally when there is a decreased mixed venous pO_2 in response to increased oxygen utilization or inadequate blood oxygen capacity, the cardiac output increases and the venous capacity decreases. These functions may be controlled by the same or different reflex or humoral mechanisms but they have a common stimulus—decreased mixed venous pO_2 . The decreased venous capacity would permit an increased cardiac output without a marked decrease in atrial and ventricular filling pressures. The net effect of these mechanisms on the atrial pressure will depend upon the adequacy of response of the heart to the stimulus. If the response of the heart is inadequate, as in acute, congestive or anemic heart failure, the net effect on venous or atrial pressure would be a marked increase.

During exercise in the normal subject again the degree of elevation of venous or atrial pressure would be dependent upon the response of the heart. In cardiac failure the net effect of exercise would be a marked increase in venous or atrial pressure since the cardiac response is inadequate while venoconstriction would be unimpaired. In individuals in whom the resting oxygen supply to the tissues was markedly decreased, as in marked cardiac failure or anemia if of a sufficient degree, the net effect on venous or atrial pressure would be a marked elevation.

The concept just postulated does not imply that a decrease in mixed venous pO_2 , *per se*, with consequent venoconstriction as in failure of oxygenation would necessarily result in an elevation of venous or atrial pressure. It would depend upon both the decrease in venous capacity and the capacity of the heart to increase its output.

In support of this concept are the experiments of Landis et al.⁵ They found that exercise in normal anesthetized dogs reduced venous pressure. If the heart were embarrassed by coronary artery ligation or atrial fibrillation, there was no elevation of venous pressure at rest. However, if these dogs were exercised, there was an elevation of atrial pressure. A diminution in cardiac competency alone left the venous pressure unaffected but in the presence of increased oxygen utilization (exercise) elevated venous pressure resulted. Starr et al.¹⁵ also have reported that in asphyxia there is an increase in the arterial and venous pressures as well as in the vigor of cardiac contraction. In discussing these experiments they say: "Such a generalized increase in intravascular pressure cannot be explained as a mechanical consequence of changes in cardiac activity and arteriolar resistance. Occurring far too rapidly to allow the assumption of an increase in blood volume with passive distention of vessels, a widespread increase in vascular tone, without compensatory relaxation elsewhere is the explanation which naturally suggests itself." Of course, an outstanding feature of

asphyxia would be a decreased mixed venous pO_2 .

Other evidence in support of this concept may be derived from studies of venous pressure during exercise in normal subjects.¹⁷ These authors report that with moderate exercise the venous pressure increases to a maximum which is maintained throughout the exercise but with heavy exercise the venous pressure increases steadily until fatigue ensues. There was a roughly linear relationship between venous pressure and work load. After exercise the venous pressure ordinarily returned to normal within a few minutes. However, after heavy work the time required for a return to the control value was often twenty-two to twenty-seven minutes. These data support the concept that venous pressure is related to the oxygen debt and, therefore, to the mixed venous pO_2 .

Results obtained in man during acute anoxia by Motley et al.¹⁸ appear to refute the concept presented herein. In five subjects breathing 10 per cent oxygen for fifteen to twenty minutes it was found at the end of this time that there was an 8.8 per cent decrease in cardiac output and a 67 per cent increase in diastolic right ventricular pressure; a slight rise in systolic arterial pressure with no appreciable change in diastolic or mean arterial pressures was also found. The average increase in cardiac rate was from a control of 67 to a rate of 80. We have calculated the mixed venous pO_2 to be approximately 24 mm Hg. The increase in diastolic right ventricular pressure may be due to an increase in mean pulmonary arterial pressure, which was found, and the slight decrease in cardiac output may have been due to a decrease in left atrial pressure. However, it is very difficult to analyze these findings with relation to the concept presented here for the arterial hypoxia certainly results in cardiovascular reflexes which may modify any effects usually produced by mixed venous hypoxia. In addition the degree of hypoxia attained in these experiments at least approaches the

previously reported critical level¹⁹ and there are no data showing progressive changes.

It is quite probable that an increase in blood volume will contribute to an elevation of atrial and venous pressure. However, the concept presented herein will explain the events seen in cardiac failure regardless of the type and etiology. The nature of the postulated reflexes or humoral mechanisms is unknown but the situation is quite analogous to that found on the arterial side—mediation of cardiac and vascular reflexes through stimulation of the chemoreceptors in the carotid body and the aortic arch.

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Seminars on Antibiotics

Dosage Forms of Penicillin for Systemic Infections*

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PENICILLIN continues to be the most widely used antibiotic agent in medical practice today. The three advances that have been made in the recent past have been the development of new dosage forms and of new salts of penicillin and a more precise definition of the indications for oral therapy. In addition further advances have been made in dosage schedules. This communication is an attempt to sum up some of the current views concerning penicillin treatment with different dosage forms.

DOSAGE FORMS FOR PARENTERAL ADMINISTRATION OF PENICILLIN

The most common dosage forms for parenteral administration are (1) sodium or potassium salts of penicillin G for injection in aqueous solution; (2) procaine penicillin G suspended in oil, water or oil and aluminum monostearate; (3) combinations of crystalline sodium or potassium and procaine penicillin for dispensing in an aqueous medium.

From the beginning of penicillin therapy the water-soluble salts have been widely used. These have been injected continuously by the intravenous or intramuscular method or, more commonly, intermittently by the intramuscular route. When the intermittent injections are used, an attempt is made by many to inject a sufficient amount at regular intervals so that penicillin is present in the blood and tissues at all times during the twenty-four-hour period. This form of treatment has been designated *continuous* peni-

cillin therapy. When penicillin is given intermittently but the injections are spaced in such a way that penicillin is not detected in the blood and tissue at all times during the twenty-four-hour period, it has been called *discontinuous* therapy. It has been recognized since the beginning of the use of penicillin that it was unnecessary to maintain a concentration of penicillin in the blood and tissues throughout the day in order to obtain optimum therapeutic results. Every infection varies in its susceptibility to penicillin so that it is not surprising that a wide variety of dosage schedules have proved to be effective. In general it can be said that the goal of treatment should be to effect recovery from infection in the shortest period of time with the least amount of inconvenience to the patient. It is for these reasons that every infection presents an individual problem.

When the aqueous soluble salts of penicillin are used in the treatment of infection, the first question to be decided is how much is to be injected in the twenty-four-hour period and how frequently should the injections be made. Inasmuch as the *minimum effective dose* has never been established for all infections it is impossible to make any precise statements about every susceptible infection. It can be said, however, that in the treatment of common infections such as pneumococcal pneumonia, hemolytic streptococcal infections and gonococcal infections the general trend in treatment with aqueous soluble salts has been to increase the amount of penicillin that is injected at each injection

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and to increase the interval between injections. For example, in the treatment of lobar pneumonia it has been found that the injection of 200,000 or 300,000 units twice daily is as effective as injecting 25,000 units every three or four hours. Thus the trend has been toward discontinuous therapy when the aqueous salts of penicillin are employed in treatment. When discontinuous treatment with aqueous preparations is used, the concentration of penicillin in the plasma and in the tissues is optimal during the first hours after injection and then declines rapidly over a period of four to six hours. When sodium or potassium penicillin G in aqueous solution is used for the treatment of infections by the discontinuous method, a decision must be made as to how much is needed during the twenty-four-hour period and how often it is to be injected. This decision will depend upon the type of infection that is being treated and the patient's response to therapy.

INDICATIONS FOR USE OF CRYSTALLINE PENICILLIN G

Crystalline penicillin G must be used for all oral therapy. It is also required in preparation of all solutions for topical application, such as intrathecal, intrapleural, intra-abdominal, intra-articular, intratracheal and in preparation of aerosol solutions.

Crystalline penicillin G should also be used parenterally in combination with procaine penicillin G in serious infections so that high plasma concentrations of penicillin may be obtained promptly. These so-called "booster" doses of penicillin may be repeated twice daily when the organisms are relatively resistant or when the infection is located in an area of the body where penicillin diffuses with difficulty.

PROCAINE PENICILLIN G

In order that the total number of injections of penicillin might be reduced to a minimum, procaine penicillin G, a salt of penicillin that is relatively insoluble in

water, was developed. This salt can be suspended in sesame oil or in water. When water is used for the suspending agent, a small amount of detergent is added to the penicillin so that it may be suspended evenly. When 300,000 units of procaine penicillin are suspended in 1 ml. of oil or water and injected into the muscles, the penicillin is slowly released from the deposit. The maximum plasma concentration of penicillin is reached within one to two hours. After this period of time the plasma concentration decreases slowly so that in practically all patients the plasma concentration will be above 0.05 units per ml. at the end of twelve hours and in at least 80 per cent of the patients for twenty-four hours. The differences between plasma concentration of penicillin when procaine penicillin or crystalline penicillin is injected are as follows: Maximum plasma concentrations following aqueous sodium penicillin G are observed within ten to fifteen minutes after injection; they are always greater than is observed following the injection of a similar amount of procaine penicillin G, but penicillin disappears from the circulating blood at a much more rapid rate. The plasma concentration of penicillin following the injection of 300,000 units of aqueous penicillin is usually about the same at the end of one hour as that which is observed at the end of twelve hours following the same dose of procaine penicillin.

In an attempt to produce an initially high plasma concentration of penicillin during the first thirty minutes to an hour crystalline sodium or potassium penicillin G has been combined with procaine penicillin G so that in 1 ml. of the aqueous material 100,000 units of the crystalline soluble salt is combined with 300,000 units of the procaine salt.

When procaine penicillin G is suspended in oil and aluminum monostearate is added, the penicillin is absorbed more slowly and more uniformly. The initial and peak plasma concentrations of penicillin are lower than when other preparations are used but plasma concentrations of 0.05

are present for a longer period of time. For example, following the intramuscular injection of 300,000 units of procaine penicillin G in oil and aluminum monostearate, the plasma concentration at the end of one hour will average 0.25 units; when this is compared with the concentration at the end of one hour following the injection of the same salt without aluminum stearate, it is found to be about one-sixth as great (average 1.5 units). The plasma concentration of penicillin usually does not decrease below 0.05 for at least ninety-six hours in most cases and this concentration is frequently maintained for as long as one hundred twenty hours. When doses of 600,000 units are injected, a relatively constant plasma concentration is maintained at a higher level over a period of four or five days but the initial plasma concentrations are not commensurately greater. All of the studies with this preparation show that it is exceedingly difficult to obtain a high plasma concentration but that the level obtained can be greatly prolonged. These observations show that procaine penicillin G with aluminum monostearate is released from tissues very slowly indeed when compared with other preparations. It can be said that following the injection of 300,000 units of procaine penicillin G in water or oil this amount is available to the tissues for a twenty-four-hour period and in a concentration that is usually considered to be adequate for controlling the vast majority of penicillin-sensitive infections. Following the injection of 300,000 units of the same salt combined with aluminum stearate, this amount of penicillin is available to the tissues over a period of ninety-six hours but the concentration of penicillin is always lower during the first twenty-four hours of treatment than when no aluminum monostearate is used.

Indications and Dosage. It is now established that a single daily injection of procaine penicillin G in oil or water is adequate for the effective treatment of most infections requiring penicillin. Larger doses, i.e., 600,000 units once or twice daily should be given in infections caused by organisms that

are only moderately sensitive to penicillin, i.e., staphylococcal infections and *Streptococcus viridans*.

When procaine penicillin G in oil and aluminum monostearate is employed the injections may be spaced several days apart. This is desirable in ambulatory patients or in mild infections when it is unnecessary to see patients every day. According to the experience of Stollerman, Roston and Toharsky,⁴ infections due to bacteria with a resistance of 0.1 unit or less may be treated with one injection of 3.0 million units since a plasma concentration of 0.1 units per ml. can be maintained for a week following such a dose. At the time their paper was published they were recommending a single intramuscular injection of procaine penicillin G with or without aluminum monostearate daily. In our own experience with hospitalized patients we have used one injection a day of procaine penicillin G in oil or water for the treatment of all moderately severe infections.

The dosage schedules of procaine penicillin G that we have used with success have been as follows: *Pneumococcus pneumonia*, 300,000 units once daily for five to seven days; *gonorrhea*, 300,000 units, one injection; *subacute bacterial endocarditis*, 300,000 to 600,000 units once or twice daily for six to eight weeks; *streptococcal infections of the throat*, 300,000 units once daily for five to seven days; *staphylococcal infections*, 300,000 to 600,000 units once or twice daily for seven to fourteen days; prophylactic use, 300,000 units once daily; postoperatively, 300,000 units daily; tooth extractions, 300,000 units once, one hour before extraction; *puerperium*, 300,000 units daily for five days; *tonsillectomy*, 300,000 units once.

ORAL PENICILLIN

Penicillin is available for oral administration in the form of either the sodium or potassium salts of crystalline penicillin. Some preparations are combined with a buffer for the purpose of increasing the stability of the product and also for its acid-

neutralizing capacity when introduced into the stomach. It has been demonstrated repeatedly that it is not necessary to use a buffered preparation in order to obtain a satisfactory therapeutic result.

More and more patients who require penicillin are receiving it by mouth. This is a logical way to give any potent drug provided it is absorbed from the gastrointestinal tract. It is convenient, it decreases nursing care and discomfort for the patient, it saves the time of the physician and nurse and it should cost the patient no more. What is of more importance is the fact that it has been demonstrated repeatedly that the oral route is as effective as the parenteral route when adequate doses of penicillin are used. The therapeutic results that follow oral therapy are comparable in every way to those following parenteral therapy in pneumococcal pneumonia, in gonorrhea, in tonsillitis, scarlet fever, erysipelas, acute otitis media due to hemolytic streptococcus, in Vincent's stomatitis and pharyngitis and in staphylococcal infections of the skin and subcutaneous tissues such as abscesses, carbuncles, furuncles, impetigo, etc. Oral therapy has another advantage in that hypersensitive reactions are less frequent than following parenteral therapy.

In the prophylaxis of gonorrhea it has been shown that one tablet of 250,000 units taken within two hours after exposure will usually prevent infection.

Dosage schedules that have been effective in the treatment of various diseases have varied greatly. In general it can be said that three to five times the minimum effective parenteral dose of penicillin has been used with a favorable result. They may be summed up as follows: Pneumococcal pneumonia, 600,000 to 1,000,000 units daily, 150,000 to 200,000 units daily in infants and children; gonorrhea, 200,000 to 500,000 units for one day; hemolytic streptococcal infections, 450,000 to 1,000,000 units daily for five to seven days; staphylococcal infections of the skin, 1,000,000 units a day for five days; Vincent's stomatitis, 400,000 to 600,000 units a day for three to four days.

CARINAMIDE

Carinamide has been used as an adjunct to penicillin therapy in order to delay its excretion by the kidney. This drug acts by inhibiting the excretion of penicillin by the renal tubules. It has been found that when 2 to 4 Gm. of carinamide are given by mouth every three or four hours the plasma concentrations of penicillin can be increased two to thirty-two fold over those obtained when the same amount of penicillin is given intramuscularly with carinamide.

This form of combined therapy has been most useful in dealing with patients who have infections due to highly resistant organisms such as are seen in occasional cases of subacute bacterial endocarditis or staphylococcal sepsis. Thus following a single injection of 500,000 units of penicillin intramuscularly and 3 Gm. of carinamide orally, plasma concentrations varying from 28 to 34 units can be maintained for a three hour period. Carinamide has been recommended by Boger and Flippin¹¹ as a valuable agent when more than 500,000 units are required daily for the treatment of any infection.

PENICILLIN DUST (INHALATION OF CRYSTALLINE PENICILLIN G)

In an attempt to treat a variety of infections of the respiratory tract, methods have been developed for inhalation of penicillin dust directly into the respiratory passages. This method of treatment was first described by Krasno, Karp and Rhoads.¹² It has been used most extensively in the treatment of patients with bronchiectasis and other chronic infections of the respiratory tract. Infections of the upper part of the respiratory tract have also been treated in this manner. In general it can be said that following the inhalation of 100,000 units of penicillin dust there is good evidence that penicillin is absorbed. Maximum levels of penicillin in the blood plasma are obtained one hour after inhalation and penicillin can be detected for three to five hours after inhalation. Cultures of the nose, throat and sputum following such therapy show a

Dosage Forms of Penicillin—Keefer

decrease in the bacterial population and in particular of the gram-positive bacteria. Hypersensitive reactions have been reported in from 3 to 6 per cent of patients. They are characterized by local reactions in the mouth and throat or at the point where penicillin comes in contact with the skin so that patients complain of stomatitis and irritation of the posterior pharynx and skin. Systemic reactions are infrequent. This form of penicillin therapy is easily available for use in office and home practice. It is usually recommended that at least one to three inhalations of 100,000 units of penicillin dust be used daily.

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Clinic on Psychosomatic Problems

Psychogenic Deafness in a Disturbed Boy

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler, and are edited by Dr. Henry H. W. Miles. This is a report of a conference of the Children's Psychiatric Service of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr. Foundation.

DR. PETER H. KNAPP: The patient (No. 540858), a nine year old boy with hearing loss, came to us through the Ear, Nose and Throat Clinic. A program of lip reading and the fitting of a hearing aid had been advised but before proceeding with the rehabilitation plan the boy's evaluation as a behavior problem had been requested. On looking over his clinic record it was noted that eighteen months previously the audiogram had disclosed only a mild left-sided hearing loss. Subsequent tests had shown loss also on the right but of a suspiciously variable and inconsistent type. Accordingly our first step was to create a friendly relationship with the boy and to re-test him. This time the audiogram was completely normal on the right, proving that he had no actual acoustic loss in that ear and that he needed not hearing rehabilitation but psychologic investigation. The mother began to bring the boy regularly to the Child Psychiatry Clinic. We will now hear the social history.

MRS. MARJORIE SPRINGER: The patient's background is a disturbed one. The mother married at nineteen when she was already three months pregnant. She never lived with her husband and was divorced from him when the patient was a year old. The father is a physician who was in the Army at the time they were married and who now practices in a western state.

After the birth of the boy the mother returned to live with her family of which the dominant figure was her mother, a stern, irritable widow. A nervous married sister, two older brothers and a twin brother were

sporadically present in the household. There was no permanent male figure in the family group. During the patient's infancy his mother was moody and depressed and the grandmother took over many of the maternal functions. The boy was in many ways quite dependent; for example, he was fed by the grandmother until he was seven years old. Despite this he attempted to fulfill a man's duties as best he knew how, trying particularly to be comforting and protective toward his mother in the increasingly frequent bitter quarrels between her and the grandmother. With his conflicts he remained emotionally dependent upon these females and was very insecure socially. He wondered about his father's unexplained absence and, not being told the true facts, developed an elaborate set of fantasies about him. Finally about a year ago his mother told him that the father would not come back eventually as the patient had wished.

The boy has always been a restless, hyperactive child and at the age of two and one-half he was described as being "inattentive" in nursery school. A factor in his insecurity may be found in the mother's periodic desire to place him in a foster home. The mother told of other incidents which seemed related to the patient's insecurity. When he was three years old he was taken to a doctor for an infected arm, was hurt by the doctor's manipulations and seemed to believe that his mother had betrayed him. At six years an even more traumatic experience occurred. He had a tonsillectomy at home. There was a long frightening wait for the surgeon to arrive and a violent

struggle before the boy could be anesthetized. Besides the tonsillectomy, a tooth extraction was done which the boy had not expected.

Following the operation a slurring of speech developed and shortly thereafter difficulty in hearing which was intermittent, variable and seemed to the mother to represent inattention. It was also about this time that the mother received the attentions of a man who was openly critical of the boy and urged her to place him in a home. The patient at this time became rebellious and quarrelsome, and his symptoms of speech and hearing difficulties grew more severe until he was finally taken to the Ear, Nose and Throat Clinic for examinations. As Dr. Knapp has mentioned, it was at first thought that his behavior problems were secondary to the loss of hearing.

My contacts with the mother were for the purpose not only to obtain historical data but also to find out about her own problems. At first she expressed much resentment toward the boy, believing that he interfered with her chances of happiness, and she expressed the desire to place him in a foster home. By the second interview, however, this desire seemed less intense. She intended breaking off her relationship with the man who, she said, did not want the boy and did not even seem to want her very much. In subsequent interviews she talked more realistically about her son and in response to encouragement in that direction expressed an increasing amount of warm feeling for him. She displayed more and more resentment toward her mother and began to think of leaving the latter's home. Although still far from emancipated, the boy's mother seems to be more comfortable, apparently as a result of her relationship to us in the clinic, and she is pleased with the boy's progress.

DR. KNAPP: The patient has been seen in ten psychotherapeutic interviews of about forty-five minutes each. The first of these served to clarify facts in the immediate history and to make friendly overtures to the boy. By the Goodenough test his in-

telligence appeared to be well above average. After the first session there was a lapse of a month because of the mother's reluctance, and then interviews were resumed at weekly intervals.

The second time he came he was friendly and very talkative, telling how he and a friend had devised a "time machine" to transport themselves into the future; they were worried, however, how to get back to the present. The patient closed with an expression of resentment against physicians mentioning his tonsillectomy and saying: "A doctor made me suffer."

He started the next session talking about a newspaper he was planning to publish on his printing press and mentioned how he played "junior commando" with a friend, going off into fantasy about how they could drop from trees onto their enemies. We played a game of checkers, the patient first insisting that there should be "no losing on purpose." He lost.

The fourth interview was begun by a request to see a laboratory which he might write up for his newspaper. He then produced some gory antivivisectionist literature and talked with abhorrence about cruelty to animals. Next he spoke more about his plans for a gigantic newspaper although he was having trouble with his neighborhood staff of twenty-five contributors. As he talked on he suddenly grew fearful, came very close to me and said that sometimes he felt like killing himself because there was a gang of bullies in the neighborhood. He would not say more but changed the subject and asked to play checkers. It was a closer game but again he lost. We ended the interview by going to see a nearby laboratory where he scrawled profuse notes for his newspaper article.

Next week he was in the laboratory before the hour, being shown around by a technician. The session began with a game of Chinese checkers which he taught me; this time I was deliberately clumsy, still he just managed to lose. During the game he commented on the heavy boots I was wearing, "just like the boots Boris Karloff wore in

"Frankenstein's Child." He told of writing to Hollywood, asking to play that role. "If I was his child, I'd be as big as I am now when I was born, and when I grew up—whew!" A little later in the game he said: "Boy, how I love to be beaten up, I mean beaten." After the game he was very restless and searched through a card file, asking if there were a "Dr. Arthur" in the hospital. His father was a doctor, he said. "They say he's out West, but I think he's right here in this hospital somewhere." He said he would never want to be a doctor, adding, however, that it would be interesting to know how to stop bleeding. At the end he expressed some resentment at having to come every week. He was encouraged to speak about his anger and urged to try weekly appointments at least once more.

During the sixth interview there were two innovations. The first was a small brown mongrel puppy which the patient had brought to the clinic, telling me that it was a female, but later referring to it by mistake as "he" and imagining the friendly little animal to be a huge, strong watchdog. The second innovation was a complicated game of checkers, devised by the patient, involving repeated crowning of Kings until eventually all that remained were two high towers of checkers. In order to terminate an endless game I let the patient win. At first he was intensely anxious but then he recovered, made me put away the checkers, as loser, and playfully threatened to strike me with a chain.

Next time, still bringing the dog, he wanted to switch seats with me and then spontaneously suggested starting our "weekly conversation." With considerable agitation he went on to talk about his mother, her demands on him, her occasional irritability and above all her quarrels with the grandmother which would make the mother cry and disturb him greatly. "Sometimes I even try not to hear her." He spoke about his fear that the women in the house would get rid of the dog and seemed reassured when I mentioned that I would take the matter up with the social worker. In a further effort

to offer support and identification I suggested that a man had to get away sometimes and that possibly it might help if he were to get off by himself a little more. At the end of the interview he grew alarmed that his mother might be able to hear him talking through the walls.

He started the eighth visit by saying: "Hi, pal," then apologized for the remark. After a preliminary game he again turned to the subject of his mother and once more showed a mounting anxiety. He spoke of how she yelled at him: "You know how women are." At one point he suddenly asked to be hypnotized; then next week he could tell me everything. The dog again figured prominently. He was worried about my suggestion of housebreaking her; he was going to hypnotize her; he put her ears back make her "look like a girl." He also tried putting his ear against the wall to find out whether this time he could hear his mother. He talked more about the situation at home, expressing concern over his mother and fear of leaving her. In closing he drew a picture of two roads, one straight stretching into the distance and one curving, coming to a dead end. He said: "I've got to decide which one to take."

Next week for the first time he seemed much quieter. He was to go to the dentist. Discussion of that led to a few more recollections about his operation. Suddenly he began drawing pictures of anger and death. He then asked whether I had a dictaphone. His suspicion and anxiety gradually diminished; he grew very friendly and talked enthusiastically about his new hobby, stamp collecting. On opening the door to leave the interview, he saw his mother in the hall and accused her: "You were listening."

In the tenth and last interview prior to the conference, we talked about the possibility of his appearing before the group. There was more talk about cruel doctors and about hypnotism. Now he wanted me to teach him hypnosis so that he could hypnotize his enemies and make them wake up friends. Again there was a spirited discussion of stamp collecting, as well as the

patient's enthusiasm for the antivivisection movement. He was distracted by the noise of a girl crying next door and stated his wish that the room were sound-proof. We parted on amiable terms and he expressed pleasure that his mother was not to be allowed at the conference.

PRESENTATION OF PATIENT

The patient was a wiry boy, very tall for a nine-year old, who was tense and physically overactive. He had been playing with a stethoscope, pretending to listen to his heart, and was embarrassed when the doctors saw him with this instrument. He spoke readily to the group but rather incoherently, the words tumbling out in a slurred way, expressing some fear and distrust of doctors in general. He was permitted to leave the room after a very brief appearance.

DISCUSSION

DR. KNAPP: In cooperation with the Ear, Nose and Throat Clinic we have been interested in the emotional aspects of deafness. We have found not only a considerable number of patients who were emotionally disturbed by their organic hearing defect but also a number in whom the primary difficulty was psychologic. So far there have been eight such cases of hysterical deafness, all of them in children. The problem, then, is by no means rare.

In presenting the case this morning I am anxious to get suggestions as to how to proceed with therapy. It seems to me that the problem is one of tremendous anxiety over growing up and uncertainty over assuming the role of a man.

DR. GEORGE CARTER: I am not sure about the mother's brother who lives with the family and is never mentioned by the patient. Is he living with them at the present time?

MRS. SPRINGER: He moved away about four months ago. The mother says that he was never a key figure in the household. Apparently he never played much with the boy and their relationship was never warm.

DR. KNAPP: The whole situation was so insecure without a father that everything has constantly conspired to drive this boy back to a state of frightened dependence on his mother, and any attempted independence seems to threaten him with losing her and to make him fear men. It would seem that disparaging remarks were often made about the absent father and thus he became a threatening figure. I should imagine that the tonsillectomy especially mobilized the fears of being mutilated and emasculated; and those fears now are very much present. I have thought that the therapeutic endeavor should be to establish a good relationship with him. Actually, with his readiness to talk one could go even further and get at the content of these fears and show him that he can grow up and still keep his mother's love and lose his fear of men. We must, however, go slowly as any mention of an operation still makes him extremely anxious. It is encouraging that he seems to want to talk about his fears and in two or three months it may be possible to deal with them. The parallel question that I would like guidance on is the question of the management of the mother because she is really in a bad situation. I think that her warm relationship to the social worker is most encouraging. We hope that she will be able to emancipate herself, set up a separate establishment and eventually make a secure independent adjustment.

DR. SAMUEL KAPLAN: I agree with Dr. Knapp's formulation of the boy's general problem. It is interesting that as far as we know this boy showed no overt difficulties in the home until the age of five. It is my belief that he must first work through the problems of being a little boy before we push him into the problems of growing up.

DR. CARTER: I am always a little confused by the use of the term "castration" as occurring in this particular situation. Obviously, the boy *does* have fears of being hurt and is afraid of hostility from the outside world. Yet, I am not quite convinced of the castration formulation and wonder about

his ambivalence in the matter of laboratories. He does not want to see animals hurt yet he wants to see where the animals are operated upon. He does not know what his role should be.

DR. KNAPP: I agree that we have no precise evidence for fears of castration but we have got evidence, I think, of his ambivalence as to what role he is going to play—the big, strong, powerful man or the role of a feminine person. You will recall his thoughts about Frankenstein's child, and how large he would be when he grew up and then contrasted with that his remark: "How I love to be beaten up." That slip of the tongue was probably not insignificant.

DR. LUCIE JESSNER: What is the grandmother like?

MRS. SPRINGER: The grandmother is sixty-five years of age, apparently in good health. She is the one who manages the household, always pays the bills and pays the rent. The mother does not even know how much the rent is. She turns over a certain amount of her pay to the grandmother who controls everything.

DR. CARTER: Would the mother be able to afford a separate home?

MRS. SPRINGER: Yes, she makes quite a good salary at the present time. Some of the mother's siblings are contributing to the grandmother's support so she can be relieved of her responsibility there.

DR. NICHOLAS D. RIZZO: I would like to ask Dr. Knapp what in his opinion was the boy using his hearing loss for?

DR. KNAPP: I do not know, except for the superficial part of it, namely, to avoid hearing unpleasant things, so to speak. In one interview in talking about the quarrels which upset him a great deal, you will remember he said: "Sometimes I even try not to hear." What the deeper meanings are I do not know. He was sent home from school originally because of his hearing loss. It seems to be tied up with the passive role he is impelled to play, namely, cutting himself off from contact with people, from activity and growth which to him are laden with anxiety.

DR. RIZZO: It is interesting that the speech difficulty was one of the reasons why the patient was referred earlier to the hospital, and his speech here before the group is similar to that of children with genuine hearing loss.

DR. EDNA SOBEL: It would seem that the tonsillectomy, hearing loss and fear of operation are linked together.

DR. GERTRUD REYERSBACH: Does it not seem that presenting a child before a group is rather a dramatic experience for him and that he may not respond the way he feels? For example, a child when asked how he is, usually answers that he is fine. At least I have generally found it so.

DR. KNAPP: In this case the boy was so eager to come and so willing to show off in a crowd that I thought he would be able to respond well.

DR. REYERSBACH: But does not bringing children into staff conferences damage the relationship between the child and the psychiatrist afterward?

DR. KNAPP: I think you are right. However, in certain cases if the preparation is good and the relationship is warm, it may be turned into a source of pleasure for him, especially in this case in which the boy was proud to think that he was important enough to come in.

DR. JESSNER: That is an interesting question since this is a very dramatic experience for a child. However, we believed that it was important for the group to see the child.

DR. SOBEL: I wonder about the hearing loss being used to cut himself off from people whom he seems to fear?

DR. JESSNER: I think his hearing is an area in which he has been tremendously frustrated. He did not hear about his father, and knows that he was kept in the dark about him for a long time. Also he did not hear in advance that his tooth would be taken out. I think that a great deal of resentment is connected with what he *does* hear and what he *does not* hear. It is encouraging that he now pays more attention to what is said in general. He did not want to hear the demands of the grandmother or to hear

in school and was not particularly anxious to hear what he *should*; in contrast, he heard only what he *wanted to hear*. I believe that by showing him the laboratory and the animals you are letting him express many of his fears. He thinks something must have been done to his body, that some function has changed so that he cannot speak and cannot hear. The fear of being mutilated is extremely strong. In the whole area of the hearing there is still much that he wants to hear, and his fantasies about his father, who is a doctor, are very important. I would give him an opportunity to talk about his father, and Mrs. Springer might sometime in her discussion with the mother find out how much he knows about the father. He has a great deal of feeling about antivivisection and when he mentions animals, he may be actually talking about himself. I would let him talk a great deal about what he thinks is done to the animals. One would get his castration fears in that form, because he must very definitely believe that he is treated like an animal to which something was done. I think, also, that his idea about hypnosis is quite important and that he believes he could tell everything about his mother through hypnosis. I wonder whether one could not explain to him the ambivalence of his feelings and that it is natural to have love and hate together. You could perhaps side with him against women at times and let him express all that he hears about animals and what he hears in regard to men. I also have a feeling that it is quite characteristic that he calls you "pal" and tries to be your equal, not only to identify himself with you but to be on an equal footing as a grown man.

FOLLOW-UP NOTE

One year after conference the boy was seen approximately thirty times. Symptomatically he was improved. His behavior at home was much better and he was doing well at school. Deafness was not a complaint although when tested at the start of the fall term he still showed some hearing loss. He described the testing afterward saying that

"some kids pretend to hear worse than they do," which was strong evidence that in some way he was himself aware of a tendency to relapse when attention was focussed on his ears in a test situation. He continued to talk about the acoustic area, speaking of his interest in radio programs, sound effects, and once putting on a ventriloquism act in which he played the part of a doctor taking care of a small patient. The importance of doctors and operations to him had been strikingly borne out by his play material. He had acted out a violent scene in which he again took the role of physician, slashed open the neck of a toy lion, talked of the risk of death from a blundering surgeon, removed "two jelly beans" and finally killed the animal. Other verbal and play productions suggested that there was a strong desire to use the psychotherapist as a model for behavior but that he was afraid of what might happen if he were to become a powerful man, whom he inevitably imagined as cruel. An effort was being made to make him clearly aware of this conflict. In that way it was believed that it might be possible to cement the symptomatic improvement, which so far depended upon continued relationship with the therapist.

A similar development was taking place in the mother who believed that the boy had "grown up a lot." She was reasonably well as long as she was in contact with the social worker. However, she was still struggling to achieve a permanent solution for her own conflicts in relation to remarriage and to her mother, which would leave her truly independent.

INTERPRETATION

Part of the discussion was in terms of psychoanalytic theory and there was some difference of opinion regarding the concept of "castration anxiety." We mention this specifically only to say that in this case terminology is unimportant. The significant points to be noted by the pediatrician, otolaryngologist or general practitioner not conversant with dynamic psychiatry can

be seen clearly by a little reading between the lines of the interview material. The temporal relationship between the tonsillectomy and onset of speech and hearing difficulties is striking. The great anxiety in the boy's mind in regard to being hurt is evident, appearing over and over again in the interviews. According to psychoanalytic theory, further investigation and elaboration of the patient's fantasies would ultimately disclose fear of loss of the penis; for the physician who is primarily interested in making the proper diagnosis and directing the patient toward appropriate therapy it is sufficient to recognize the fact that the fears of bodily injury or mutilation are important.

The dynamic structure of the problem in an oversimplified scheme can be seen as follows: Without a father and in the face of great insecurity, the boy was forced into a dependent attachment to his mother. The father was a physician and we know that the boy heard disparaging remarks about him. It would not be taking a long step to suppose that the little boy feared this absent, threatening, doctor father. (He resented his father's desertion, and hostility in a child's mind is associated with fears of reprisal.)

Thus when operated upon and particularly when something was done to him without warning, the patient's fears of mutilation were demonstrated to him as *reality*. It is very probable that in his fantasies, "doctor" and "father" were equated, both being fearful and cruel persons.

The treatment process was presented in some detail to illustrate the teamwork of psychiatrist and social worker. In psychotherapy with children it is advisable, if not imperative, that the mother be helped to understand her own problems, since it is so often in the mother-child relationship that the roots of the trouble lie. The interview

material may have seemed diffuse and incoherent. One must remember that in dealing with children a full and connected story cannot be obtained, and one depends to a large degree upon indirect evidence based upon the child's actions, fantasies, hobbies, artistic productions, etc. For example, this boy's fears of being injured or mutilated are revealed obliquely in his preoccupation with vivisection.

In psychiatric work with children it is by no means uncommon to see problems involving fears of bodily injury activated or intensified following an operation. It is now generally accepted that tonsillectomy (or other operative procedure) should be postponed, unless there are urgent indications, until the child is at least eight years old. When an operation has to be done, the patient should be prepared by telling him in advance what will happen, by giving adequate reassurance, having his mother with him when he awakens from the anesthesia, etc.

As this case illustrates it may not be necessary to analyze in detail all the ramifications of the child's conflicts. The satisfactory therapeutic result was probably due to: (1) the secure relationship which the boy developed with the male therapist who provided a satisfactory masculine figure with whom to identify, and (2) the increased warmth and affection which his mother was able to give him, achieved through her contacts with the social worker.

The question of a specific diagnosis was not mentioned. The neurotic problems of children usually do not fit the conventional clinical patterns which are described for adult psychoneurosis. From a practical standpoint, certainly, the attaching of a descriptive label is far less important than an understanding of the dynamic mechanisms of the illness.

Clinico-pathologic Conference

Cardiac Failure, Elevated Basal Metabolic Rate and Psychosis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. S., (No. 156162), was a white, married housewife, fifty-six years of age, who entered the Barnes Hospital for the first time on January 4, 1948, complaining of "a sensation of choking" and dyspnea on exertion. The family history was of interest in that her father and one brother had had heart disease. Four of her father's immediate relations had had "a goiter" and one of them had been subjected to surgery.

Three times during her childhood the patient had pneumonia. When she was twenty-two, six months after her third pregnancy, she developed pain in the left chest and a cough which lasted three weeks. She apparently recovered from this illness and was well until the age of thirty-five at which time she had "a nervous breakdown" which lasted several weeks; its onset followed shortly after the birth of her eighth child. At the age of forty-nine she received a series of injections of an unknown type for marked stiffness of the joints of her left hand, and when she was fifty-four she developed soreness and stiffness of her shoulder joints.

During her sixth pregnancy the patient became aware of enlargement of her neck. Concomitantly she had the first of a series of "choking sensations" which she could not further describe except to state that she was relieved when she lay flat in bed. Similar episodes occurred in each of her four succeeding pregnancies and occasionally between them, but the size of her neck did not

change since she first noted it to be enlarged. One year before entry the patient noted onset of dyspnea on exertion as well as of paroxysmal nocturnal dyspnea. The nocturnal attacks began to appear with increasing frequency and the patient developed a dry, annoying cough. Two weeks before entry her ankles swelled and she was forced to wear rubber stockings. The attacks of paroxysmal nocturnal dyspnea became so severe that she was forced to sleep sitting up in a chair. She was seen by a physician who told her that she had "an inward goiter" although at no time had she experienced difficulty in swallowing. Although her appetite had been good, she had had no evidence of excessive nervousness. During the four years prior to admission she had lost 28 pounds in weight and had noted increased ease of fatigability but at no time did she perspire excessively nor had she had precordial pain. Three weeks before she came to the hospital her physician prescribed 15 drops of a bitter, dark liquid to be taken every four hours. She took this preparation for two weeks. When she was seen in the out-patient clinic several days before admission, she was advised to take digitoxin instead of the liquid medicine.

At the time of entry her temperature was 38.2°c., pulse 100, respirations 24 and blood pressure 180/96. The patient was well developed and well nourished but because of dyspnea she sat propped up in bed. The skin was smooth and of fine texture but no

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

perspiration was apparent. There were many varicose veins over both legs. The pupils reacted normally to light and accommodation and the fundi showed only mild sclerosis of the vessels. There was no lid lag, stare or inability to converge. The mouth was edentulous. A large, firm, slightly nodular mass was present on the right side of the neck anteriorly and its lower border could be defined above the clavicle. The thyroid isthmus was palpable and the left lobe of the thyroid gland was barely discernible. There was no bruit. The trachea was in the midline. The neck veins were dilated and engorged, particularly on the right. Examination of the lungs revealed them to be clear to percussion and auscultation. The left border of cardiac dullness was 11 cm. to the left of the mid-sternal line in the fifth interspace. There was slight right border enlargement. A loud, harsh grade III systolic murmur was heard at the aortic area but it was not transmitted. A grade II early diastolic murmur was heard over the aortic area and along the left sternal border. P_2 was accentuated. At the mitral area there was a grade II systolic murmur and a low pitched rumbling mid-diastolic murmur which was heard best when the patient lay on her left side. There were no thrills. The rhythm was regular and the sounds were of good quality. The liver edge was palpable 4 cm. below the right costal margin and was slightly tender. The spleen could not be felt. There was 1+ pitting edema of the lower extremities. The patient exhibited no tremor of the outstretched hands and the neurologic examination was within normal limits.

The laboratory data were as follows: Blood count: red cells, 4,580,000; hemoglobin, 14.5 Gm. per cent; white cells, 9,800; differential count: eosinophiles, 1 per cent; stab forms, 3 per cent; segmented forms, 75 per cent; lymphocytes, 19 per cent; monocytes, 2 per cent. Urinalysis: albumin, trace, otherwise negative. Stool examination: negative. Blood Kahn test: negative. Venous pressure: 225 mm. of saline. Circulation (decholin) time: 21 to

28 seconds, (end point not definite). Blood chemistry: non-protein nitrogen, 22 mg. per cent; total protein, 6.0 Gm. per cent; albumin, 3.8 Gm. per cent; globulin, 2.2 Gm. per cent; chlorides, 105 mEq./L.; icterus index, 14 units; cephalin-cholesterol flocculation test, negative; thymol turbidity test, 1.9 units. Roentgenogram of the chest: "There is second degree cardiac enlargement. The aorta is tortuous and there are increased lung markings suggestive of pulmonary vascular congestion." Electrocardiogram: ST segment slightly depressed in leads I and II, T waves diphasic in leads I and II and inverted in CF_4 .

Two days after entry the attending physician described a systolic thrill over the aortic area. Otherwise the signs were unchanged except that the patient had become afebrile. She was completely digitalized, was given diuretics and placed on a low salt diet. Fluoroscopy with a barium swallow did not reveal left auricular enlargement. After the patient had achieved compensation the basal metabolic rate was +55. The blood cholesterol was 218 mg. per cent. On the tenth hospital day the patient was ambulatory. During the ten days she had lost 9 pounds in weight. The cardiac signs were as on entry except that the mitral diastolic murmur could no longer be heard. A radioactive iodine excretion test was performed and it was found that 80 per cent of the ingested dose was excreted. Just prior to discharge on March 13, 1948, the mitral diastolic murmur was again heard, sharply localized over the apex. The patient left the hospital to follow a therapeutic regimen designed to preserve her cardiac status; in addition she was given potassium iodide.

Following discharge she was seen regularly in the endocrine clinic. One month after she left the hospital, during which time she had taken potassium iodide steadily, her basal metabolic rate was found to be +48. Prophylthiouracil therapy was instituted, a dose of 50 mg. five times a day being given. When she returned to the clinic on May 23rd, she had gained 1½ pounds

in weight. She was given mercurhydrin and sent into the hospital that day.

At the time of entry her temperature was 38°c., pulse 84, respirations 24 and blood pressure 140/80. The significant changes in physical findings from the first admission were as follows: The trachea appeared to be pushed to the left. The systolic thrill over the aortic area was easily palpable when the patient sat erect and the aortic systolic murmur was now transmitted to the neck. The rumbling, low pitched, mid-diastolic murmur at the apex was easily audible and there were a few rales at the lung bases. The liver was enlarged and there was moderate peripheral edema.

The laboratory findings were normal with the following exceptions: The urine showed 2+ albuminuria. The venous pressure was 235 mm. of saline, the circulation time with decholin, 24 to 27 seconds. The non-protein nitrogen was 24 mg. per cent, the basal metabolic rate +22, the blood cholesterol 202 mg. per cent.

The patient was again treated for cardiac decompensation; she improved rapidly, becoming asymptomatic in several days. She left the hospital on May 29, 1948, to be followed in the clinic. She was seen in the endocrine clinic on June 10th and was given 10 mc. of radioactive iodine. She remained quite well for two weeks; then once again dyspnea on exertion appeared. Three days before her third admission dyspnea became marked and the onset of orthopnea was noted. She was re-admitted on July 10, 1948. Her temperature was 38.2°c., pulse 44, respirations 22 and blood pressure 170/100. The physical findings were essentially the same as on the second admission. The laboratory findings likewise were unchanged except that the patient now had 3+ albuminuria.

On the second hospital day the patient was noted to have an apical rate of 48 with runs of extrasystoles. An electrocardiogram revealed frequent premature ventricular contractions with bigeminy. The basal metabolic rate was +19 and reduction in the size of the right lobe of the thyroid

gland was noted. When she left the hospital on July 15, 1948, no further therapy for thyrotoxicosis was prescribed. About five weeks after discharge on August 21st the patient was seen in the clinic at which time her basal metabolic rate was +40. At that time she was given 5 mc. of radioactive iodine. When she returned on September 21st her basal metabolic rate had risen to +47. During the interval she had done well but just before returning to the clinic she had a rather sudden re-appearance of dyspnea and recurrence of edema. She had continued to take digitoxin, to follow a low salt diet and receive mercurhydrin regularly in the medical clinic. She was re-admitted for the last time on September 21, 1948.

Physical examination revealed the temperature to be 37.8°c., pulse 64, respirations 32 and blood pressure 130/85. The patient was now poorly nourished, appeared chronically ill and was markedly dyspneic. The right lobe of the thyroid gland measured approximately 3 by 4 cm. The trachea was deviated to the left. There was impaired resonance to percussion over the right base and rales were heard in this area. Cardiac examination was unchanged. There was 3+ pitting edema of the legs.

Laboratory data were as follows: Blood count: within normal limits. Urinalysis: albumin, 2+, centrifuged sediment, 20 to 30 white cells, occasional red cells and hyaline casts per high power field. Blood chemistry studies: within normal limits. Blood cultures: negative. Electrocardiogram: ST segments depressed in leads I, II and CF_4 ; PR interval 0.19; T waves inverted in leads I, II, and CF_6 ; occasional ventricular premature contraction; left axis deviation. Venous pressure: 182 mm. of saline. Circulation time: 50 seconds.

The patient was fluoroscoped and the heart was noted to be greatly enlarged both to the right and to the left. It was boot-shaped in contour. A barium swallow indicated slight enlargement of the left auricle. On the third hospital day the patient's temperature rose to 38.4°c. The chest signs remained unchanged. A chest x-ray re-

vealed small rounded areas of infiltration at the right base considered to represent early pneumonia. Penicillin therapy was instituted. One week after admission the patient suddenly became markedly disoriented and exhibited definite paranoid trends. Sometimes she was uncommunicative and at other times agitated. During the second week of the hospital stay she became even more disturbed. A lumbar puncture was performed and an initial pressure of 220 mm. and a final pressure of 145 mm. of water were recorded. The spinal fluid findings were entirely negative. The patient exhibited periods of delirium and on careful questioning her family stated that she had behaved abnormally on occasions just before her admission. A psychiatric consultant was called and made diagnoses of delirium, unstable personality and paranoid tendencies. The patient continued to have a slight elevation of temperature. Repeated blood cultures were negative and significant numbers of red cells did not appear in the urine. By the end of the third week, although the patient's cardiac status had markedly improved, she became more difficult to manage and was transferred to the neuropsychiatric service. On the next day her temperature rose to 39.6°C., her white count to 26,400 and the differential count showed 92 per cent segmented forms. She became semicomatose and was transferred back to the medical service.

Physical examination revealed definite signs of consolidation of the right lower lobe and streptomycin therapy was instituted. Penicillin had been continued throughout this previous period. Further blood cultures were negative. Sputum examination revealed cocci and chains in pairs. The non-protein nitrogen had risen to 80 mg. per cent. The chlorides were 96 mEq./L. and the icterus index 30 units. Sodium bilirubinate was 1.9 mg. per cent, the bilirubin-globin 1.9 mg. per cent, with a total of 3.8 mg. per cent. Because the diagnosis of pulmonary infarction was seriously considered, dicumarol therapy was begun and the prothrombin time was lowered to 30 per cent

of normal. On October 15th, about three and one-half weeks after entry, the patient's icterus index had risen to 40 but jaundice was not clinically discernible. Although the patient became more alert and her strength increased, her psychotic state again became pronounced. During the fifth week her temperature which had fallen to normal again began to spike despite the fact that she was still receiving both streptomycin and penicillin. At this time her icterus index was 24 units. The heart sounds became weaker and the blood pressure fell somewhat. The pulmonary signs were unchanged but her white count had fallen to 11,400. Sputum cultures were positive for coliform organisms. Edema of the ankles increased and there was marked calf tenderness. The patient's agitation became extreme and it was very difficult to control her. Just before she died she had periods of transient auricular fibrillation. She became unresponsive and expired quietly on October 27, 1948.

CLINICAL DISCUSSION *

DR. W. BARRY WOOD, JR.: The resident has chosen an extremely difficult and complicated case for discussion today. In our discussion we must consider the cardiovascular system, the thyroid gland, the pulmonary lesion and finally the psychosis which made management of this patient so difficult for the house staff. Since the cardiac disease probably represents the most straightforward aspect of this case, it might be well to begin with that phase of this patient's illness. Mr. Lund, would you discuss the nature of the cardiac involvement?

MR. ROBERT H. LUND: The duration of the patient's illness and the physical findings suggest that she had aortic stenosis and aortic insufficiency. Whether she had mitral stenosis is not as clear to me although I think it is entirely conceivable that the mitral valve was involved.

* It should be noted that this clinico-pathologic conference differs from those usually published in the Journal in that the discussion was carried on by students selected from the Senior class rather than by members of the faculty.

DR. WOOD: To what etiologic factor do you ascribe aortic stenosis and insufficiency?

MR. LUND: I believe this patient had rheumatic heart disease. There is no history of acute rheumatic fever but its absence does not particularly disturb me in making such a diagnosis. One must also consider arteriosclerosis of the valve in passing, but no mention was made of calcification of the aortic valve in any of the x-rays; the fact that no calcification was described does not rule it out.

DR. WOOD: Mr. Rosecan, do you expect the pathologists to demonstrate calcium in this patient's valve?

MR. MARVIN ROSECAN: Yes, Dr. Wood, I do. A series of 107 cases of aortic stenosis was recently reported by Kumpe and Bean;¹ calcium was demonstrated in the aortic valve at autopsy in every one of the 107 hearts.

DR. WOOD: That was indeed a most striking finding. The monograph to which you refer is an excellent review on all aspects of aortic stenosis and as you point out every one of the hearts studied by the authors showed calcium in the aortic valve at autopsy either grossly or microscopically. Thus one would certainly be on safe grounds if he states that the pathologists will demonstrate calcium in this patient's valve. You agree then with Mr. Lund's preliminary diagnosis.

MR. ROSECAN: Yes, I do.

DR. WOOD: Let us assume then that this patient probably had rheumatic heart disease with calcific aortic stenosis. Mr. White, what about mitral valve involvement?

MR. LAURENS T. WHITE: It is entirely possible that this patient will have no actual mitral disease. Again in their monograph on aortic stenosis, Kumpe and Bean included only those cases of aortic stenosis which were "uncomplicated by deforming lesions of other valves," that is, aortic valvular disease without significant mitral involvement. Eighty-two per cent of the

¹ KUMPE, C. W. and BEAN, W. B. Aortic stenosis: a study of the clinical and pathologic aspects of 107 proved cases. *Medicine*, 27: 139, 1948.

patients had a mitral systolic murmur and slightly less than 30 per cent a mitral diastolic murmur. Considering that observation and the additional fact that this patient did not have particularly striking left auricular enlargement, I would predict that even if she did have mitral stenosis it was minimal.

DR. WOOD: In other words, if this patient did not actually have mitral stenosis the murmur was a so-called Austin-Flint murmur. Mr. Au, from a statistical standpoint, assuming that this patient does have rheumatic heart disease, is it more likely that the mitral valve would also be involved?

MR. MAN HING AU: Involvement of both the aortic and mitral valves is more common than involvement of the aortic valve alone.

DR. WOOD: Then you disagree with Mr. White.

MR. AU: I believe the patient probably had involvement of the mitral valve although it may have been minimal. According to Clawson, Bell and Hartzell,² who studied a group of 130 patients with chronic endocarditis, fifty had involvement of both the aortic and mitral valve whereas the mitral valve alone was affected in forty-four and the aortic valve alone in thirty-two.

DR. WOOD: Can you meet Mr. Au's argument, Mr. White?

MR. WHITE: I am not anxious to take issue with him. I cannot say that the mitral valve was not involved; I merely state that it does not have to be involved.

MR. STANLEY L. LONDON: When this patient was admitted for the first time, a mitral diastolic murmur was described. Following complete digitalization the murmur disappeared. Had this patient had an organic lesion of the mitral valve one would not expect the murmur to disappear completely under those circumstances. On the other hand, if the mitral stenosis was relative, that is, due to enlargement of the left ventricle after digitalization, with decrease

² CLAWSON, B. J., BELL, E. T. and HARTZELL, T. B. Valvular diseases of the heart with special reference to the pathogenesis of old valvular defects. *Am. J. Path.*, 2: 193, 1926.

in the size of the left ventricle, the murmur might well have disappeared.

DR. WOOD: In other words, you suggest that the murmur was not organic.

MR. STANLEY N. ROKAW: It should be pointed out that the murmur later reappeared, and I believe it is a well established clinical fact that the diastolic murmur of mitral stenosis may appear, disappear and reappear depending upon the functional state of the heart.

DR. WOOD: Your point is well taken. The murmur of mitral stenosis may change in intensity or actually disappear with a change in the heart rate, rhythm or other factors. Therefore, I think, Mr. London, that one cannot rule out an organic lesion because of the ephemeral nature of the murmur. A similar sequence may be observed with aortic diastolic murmurs although it is less common. As has been pointed out a diagnosis of mitral stenosis cannot be made dogmatically but it probably was present.

MISS ELIZABETH HAPPEL: It is of interest that in Karsner's series of 200 cases of calcific aortic disease,³ of eighteen patients with presystolic mitral murmurs, fifteen had deforming mitral stenosis at autopsy, whereas of fifteen patients who had a mid-diastolic murmur only nine had deforming mitral stenosis. The fact that this patient's murmur was mid-diastolic in time may, on the basis of Karsner's experience, lessen the likelihood of her having organic mitral stenosis.

DR. WOOD: In other words, the timing of the murmur may be of some import in deciding whether or not it is organic.

MISS HAPPEL: Yes.

DR. WOOD: What do you think about this point, Mr. Berg?

MR. LEONARD BERG: I think it sounds logical, Dr. Wood. I believe it is also worth mentioning that the absence of chronic auricular fibrillation so often associated with rheumatic mitral stenosis and the absence of the high peaked or split P waves which

³ KARSNER, H. T. and KOLETSKY, S. Calcific Disease of the Aortic Valve. Philadelphia, 1947. J. B. Lippincott Co.

are common in the electrocardiogram of patients with organic mitral valvular disease make one question the diagnosis of organic mitral stenosis.

MR. THOMAS J. WALSH, JR.: It seems to me that one must emphasize the fact that changes in the left ventricle itself may modify the character of the murmur of mitral stenosis so that none of the previously mentioned points can be applied in an all or none fashion.

DR. WOOD: It is apparent that there is a definite division of opinion about the question of mitral stenosis and since only the pathologists can settle this question I should like to go on and ask Mr. Heideman whether he thinks any other cardiac lesion need be considered.

MR. MILO L. HEIDEMAN, JR.: Late in this patient's course she developed a rather slow cardiac rate and runs of ventricular extrasystoles; I wonder whether myocardial damage and consequent interference with the conduction system may have developed because of coronary artery involvement. Digitalis may have had a role in these changes.

DR. WOOD: One must certainly consider abnormalities of the coronary circulation in view of the fact that the patient had severe aortic valvular disease; it is well known that aortic valvular disease may in its progression involve the coronary ostia. Further, a patient in this age group may have coronary sclerosis *per se*. What was the relation, if any, of coronary sclerosis to calcific aortic disease in the patients from the Cincinnati General Hospital?

MR. ROKAW: The authors specifically made the point that although coronary sclerosis occurred in a high percentage of their patients, the degree of coronary sclerosis could not be correlated with the extent of aortic valvular sclerosis. In some of their patients calcification of the aortic valve did progress to the point where the ostia of the coronary vessels were involved as you have just indicated.

MISS HAPPEL: In Karsner's series 51.5 per cent of the patients died in an episode of

congestive failure. Although twenty-three of the 200 patients died suddenly, syncope occurred in only three. These observations seem at odds with those generally held previously.

MR. LUND: I should like to mention the possibility that the patient may have had a bicuspid aortic valve.

DR. WOOD: Your suggestion is a good one. Could a bicuspid valve give rise to these signs?

MR. LUND: It certainly may be associated with both systolic and diastolic aortic murmurs.

DR. WOOD: Let us now turn to the possible thyrotoxicosis. This patient's thyroid gland was said to have been enlarged and nodular. Although the basal metabolic rate was very high, the cholesterol was never depressed. Furthermore, the results of the study of radioactive iodine excretion were not impressive on the one occasion that the test was performed. Mr. Schulz, do you believe that Dr. Moore will show us a toxic nodular goiter or will this be a nodular thyroid without evidence of activity?

MR. DALE M. SCHULZ: I believe that all of the findings can be explained on factors other than thyrotoxicosis and do not think that she had that disease. Her response to therapy was not impressive.

DR. WOOD: I think you can defend your hypothesis very well but how do you account for the high basal metabolic rate?

MR. SCHULZ: In aortic stenosis *per se* the basal metabolic rate can be quite elevated.

DR. WOOD: Can anyone comment on the relation of aortic stenosis to an elevated basal metabolic rate? Are you familiar with that subject, Mr. Levitt?

MR. JOSEPH LEVITT: Dr. Levine described this entity recently.⁴

DR. WOOD: Yes, in 1947 Levine reported four cases of aortic stenosis and in all of these the patients exhibited the clinical picture of hyperthyroidism. All four at post-mortem examination had normal thyroids.

⁴ SMITH, J. A. and LEVINE, S. A. Aortic stenosis with elevated metabolic rate simulating hyperthyroidism. *Arch. Int. Med.*, 80: 265, 1947.

Can anyone comment on the pathologic physiology of this syndrome? Why should the basal metabolic rate be elevated in aortic stenosis?

MR. WALSH: In that article it was postulated that the hypertrophy of the ventricle might explain the increased oxygen utilization. Levine found that in his four patients the average weight of the hearts was approximately 500 Gm. To test his hypothesis he studied another group of hearts from patients with aortic stenosis without elevated basal metabolic rates. The hearts from this second group of patients weighed on the average approximately 533 Gm. In order to make the original theory sound one would have to assume that the patients in the second series were all hypothyroid. Since this assumption is not tenable, the pathologic physiology of the syndrome remains unexplained.

DR. WOOD: You have summarized the situation well, Mr. Walsh. What explanation do you offer for the elevation of the basal metabolic rate?

MR. WALSH: Congestive heart failure elevates the basal metabolic rate.

DR. WOOD: On the other hand, the basal metabolic rate was elevated even when the patient was compensated. Will anyone defend the position that this patient indeed had hyperthyroidism?

MR. ROKAW: It seems to me, Dr. Wood, that one cannot disregard without serious consideration the combination of factors here. I should like to review them. This patient had a persistently elevated basal metabolic rate. It is true that her blood cholesterol was not low but many investigators have found that the cholesterol level does not always follow closely fluctuations in thyroid activity. The excretion of 80 per cent of the ingested radioactive iodine is likewise against a diagnosis of hyperthyroidism, but this patient had previously received iodine therapy and Means and others have found that not only can one change the metabolism of a given dose of radioactive iodine but also one can increase the serum protein-bound iodine in such patients merely

by giving Priodax for a cholecystogram. This tracer dose was given within three weeks of the termination of therapy with Lugol's solution; this fact may have accounted for the relatively high excretion of radioactive iodine. The patient had lost 15 pounds during the course of her illness and she had the fine skin of the thyrotoxic patient. No eye signs were described. Although it is stated in the protocol that she did not sweat excessively, some of the people who saw her on the ward report that on occasion she sweated profusely. Her very rapid pulse rate could have been explained on the basis of cardiac decompensation. Finally she had definite enlargement of the thyroid gland. One cannot state with much assurance whether the thyroid gland was hyperactive or not.

DR. WOOD: Although there was definite doubt on the part of the staff as to whether this patient did have hyperthyroidism she was treated as though she did. Mr. London, if you had been the medical house officer in charge of this patient, would you have done differently?

MR. LONDON: I think I would have treated her essentially the same way. One could not rule out thyrotoxicosis and since part of the clinical picture of congestive failure may have been due to hyperthyroidism, one certainly was justified in treating the patient in the manner described. I actually do not believe that she had thyrotoxicosis.

DR. WOOD: Mr. Levitt, what would you say about treating a patient with chronic cardiac failure for hyperthyroidism even though she were apparently euthyroid?

MR. LEVITT: It has been shown that digitalis will exert a greater effect in patients with thyrotoxic heart disease if the thyrotoxicosis is controlled first. If I suspected that the patient were the least bit hyperthyroid, I would attack that aspect of the problem first.

MR. ROKAW: Some years ago thyroidectomy was performed on patients with severe cardiac failure whether they had thyrotoxicosis or not.

DR. WOOD: Dr. Blumgart⁵ was one of the first advocates of that procedure and at the recent meetings of the Association of American Physicians Dr. Blumgart⁶ again reported on the use of I¹³¹ in the treatment of chronic congestive heart failure. On the basis of that work it would seem reasonable to have treated this patient with radioactive iodine whether or not she was hyperthyroid. Actually there was little response to therapy as evidenced by determinations of the basal metabolic rate. As with the problem of mitral stenosis we cannot say with confidence whether this patient's thyroid gland was hyperactive or not. Conceivably the signs of hyperthyroidism may have been due to aortic stenosis *per se*.

MR. LEVITT: In a patient whose nodular goiter increases in size under observation one cannot rule out carcinoma completely.

DR. WOOD: That diagnosis would have to be considered. Do you think it is likely?

MR. LEVITT: Not likely but there is a possibility.

DR. WOOD: Recently at a meeting of the Washington University Medical Society we were reminded that a significant number of patients with thyroid nodules develop "carcinomatous degeneration." Perhaps Dr. Robert Moore will show us a malignant change here.

MR. ROKAW: May we ask Dr. Grunow if the pulmonary lesion conceivably could have represented a metastasis?

DR. OTTO H. W. GRUNOW: The pulmonary findings from the radiologic point of view were much more in keeping with either pneumonia or pulmonary infarction.

DR. WOOD: Dr. Heideman, what two pulmonary lesions would you consider primarily?

⁵ BLUMGART, H. L., LEVINE, S. A. and BERLIN, D. D. Congestive heart failure and angina pectoris, therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity. *Arch. Int. Med.*, 51: 866, 1933.

⁶ BLUMGART, H. L., FREEDBERG, A. S., KURLAND, J. and URELES, A. L. Treatment of intractable angina pectoris and congestive failure in euthyroid patients by producing hypothyroidism with I¹³¹. *Tr. A. Am. Physicians*, to be published.

MR. HEIDEMAN: Bacterial pneumonia and pulmonary infarction.

DR. WOOD: Yes, pulmonary infarction is common in congestive heart failure and so is bacterial pneumonia. Which do you believe was present here, Mr. Heideman?

MR. HEIDEMAN: I believe the fact that the patient developed fever, leukocytosis and a left shift in the differential at the time when the pulmonary findings increased suggests pneumonia rather than pulmonary infarction.

DR. WOOD: On the other hand, jaundice makes one think of pulmonary infarction.

MR. HEIDEMAN: I do not see why the direct bilirubin would be elevated in that case.

DR. WOOD: No, that particular result is not explicable on the basis of a diagnosis of pulmonary infarction.

MR. LONDON: The patient's liver function may have been deranged because of chronic congestive failure and development of cardiac cirrhosis.

DR. WOOD: Let us now consider the problem of this patient's psychosis. It was a very serious complication of her illness and suggests several explanations.

MR. WHITE: Conceivably, the psychosis may have been associated with aortic stenosis. In 5 to 10 per cent of patients with aortic stenosis there is accompanying mental aberration which cannot always be correlated with pathologic findings in the brain. Second, patients who have had cerebral thromboses may have subsequent degeneration of cerebral tissue and become psychotic. Finally this patient may have had a so-called "cardiac psychosis," which not uncommonly develops in patients with cardiac failure as they are becoming compensated.

DR. WOOD: Mrs. McChesney, which diagnosis do you favor?

MRS. MARGARET B. MCCHESNEY: I remember seeing this patient on the ward. The psychosis was quite striking and most of us who saw her believed that the clinical picture was representative of cardiac psychosis. As has been pointed out cardiac psychoses often develop as the patient's

cardiac failure improves, and that situation obtained here.

DR. WOOD: Cardiac psychosis must certainly be seriously considered. As Mr. White suggested, however, aortic stenosis also looms as an important possibility on the basis of the findings in Kumpe and Bean's series. Some of these patients develop psychoses because of cerebral anoxia due to the obstruction of cardiac output by the stenotic valve; in others there may be vascular disease of the brain. Will Dr. Moore show us any pathologic lesion in the brain?

MRS. MCCHESNEY: In true cardiac psychosis I doubt that pathologic findings are demonstrable. I should like to mention one other possibility, however. This patient may have had carcinoma of the thyroid with metastatic cerebral lesions.

DR. WOOD: Yes, that is a possibility. In summary, it seems to me that most of us agree that this patient had rheumatic heart disease which involved the aortic valve. As so often happens the patient did well until she reached her sixth decade. Then her cardiac function became seriously impaired and the patient developed symptoms of congestive heart failure. Whether or not she had mitral stenosis remains a question for the pathologists to settle. Statistically she should have it but it is conceivable that the mitral diastolic murmur described was of the so-called Austin-Flint type. Whether the nodular goiter which was palpable was toxic cannot be stated; the manifestations of thyrotoxicosis could have been due to aortic stenosis. The pulmonary lesions may have been either bronchopneumonia complicating pulmonary infarction or congestive heart failure. Again, we are unable to state which one was responsible although I believe we lean toward bronchopneumonia. There are two good explanations for the psychosis and it remains to be determined whether Dr. Moore will demonstrate encephalomalacia. Are there any other possibilities?

MR. BERG: It has recently been pointed out that patients with rheumatic heart

disease may at autopsy exhibit lesions of the cerebral vessels which resemble the lesions in rheumatic carditis and which may or may not cause symptoms. Such lesions could have been responsible for this patient's psychosis.

DR. WOOD: Are you referring to rheumatic encephalitis?

MR. BERG: The process is not primarily encephalitic but rather vascular in nature with secondary encephalomalacia. Whether or not it represents a definite rheumatic lesion is doubtful.

Clinical Diagnoses: Rheumatic heart disease with aortic stenosis, aortic insufficiency and ? mitral stenosis; congestive heart failure and chronic passive congestion; nodular goiter, ? toxic; bronchopneumonia, ? pulmonary infarction.

PATHOLOGIC DISCUSSION

DR. F. BERTOLI: At autopsy there was distinct pallor of the skin and mucous membranes and marked persistent pitting edema of the lower extremities.

The thyroid gland weighed 40 Gm. The left lobe was small and contained prominent follicles. Almost entirely replacing the right lobe was a smooth, ovoid, encapsulated nodule 3 cm. in average diameter. The peripheral areas were yellow gray, hard and surrounded by a fibrous capsule 1 or 2 mm. in thickness.

The heart was markedly enlarged, weighing 710 Gm. There was a small amount of fluid in the pericardial cavity and focal areas of fibrous thickening of the pericardium. Hypertrophy of the myocardium, especially of the left ventricle and left atrium, was prominent. The aortic orifice was markedly narrowed by two partially fused coronary cusps with an incomplete raphe; the posterior cusp was wider than normal. The cusps were thickened by small yellow gray, irregular, brittle nodules. A round defect, $\frac{1}{2}$ cm. in diameter, with smooth rounded edges was present in the posterior cusp. At the apex in the left ventricle there was an oval, gray, firm mass 1.5 by 1 by 0.5 cm. in its dimensions. Its surface



FIG. 1. The aortic valve with calcified masses on the coronary cusps and a circular defect in the posterior cusp. Note the absence of arteriosclerosis in the aorta.

was trabeculated and it was firmly attached to the endocardium which was markedly thickened, white and smooth in the adjacent area. Beneath this thrombus the myocardium was thin with a fibrous scar extending through the septum and the right ventricular wall. Attached to the scar in the right ventricle there was a similar but smaller thrombus.

The lungs were of increased weight. A few fibrous pleural adhesions were present and in the lower lobe of the right lung there were numerous bulging, wedge-shaped, dark red, elevated, dry, well defined foci measuring 1 to 4 cm. in diameter; there was a finely granular deposit on the overlying pleura. About these infarcts were foci of firm, gray, granular bronchopneumonia. The remaining portions of the lungs were brown red, smooth, normally crepitant and exuded a moderate amount of thin frothy fluid on pressure. In the lumina of the secondary and tertiary branches of the pulmonary artery leading to the right lower lobe there were several dark red, friable thrombi.

Except for an infarct in the upper pole of the spleen and congestive changes in the liver and spleen, the other viscera including the brain were not grossly remarkable.

DR. ROBERT A. MOORE: The first photograph (Fig. 1) is of the heart. There were calcified masses within the substance of the

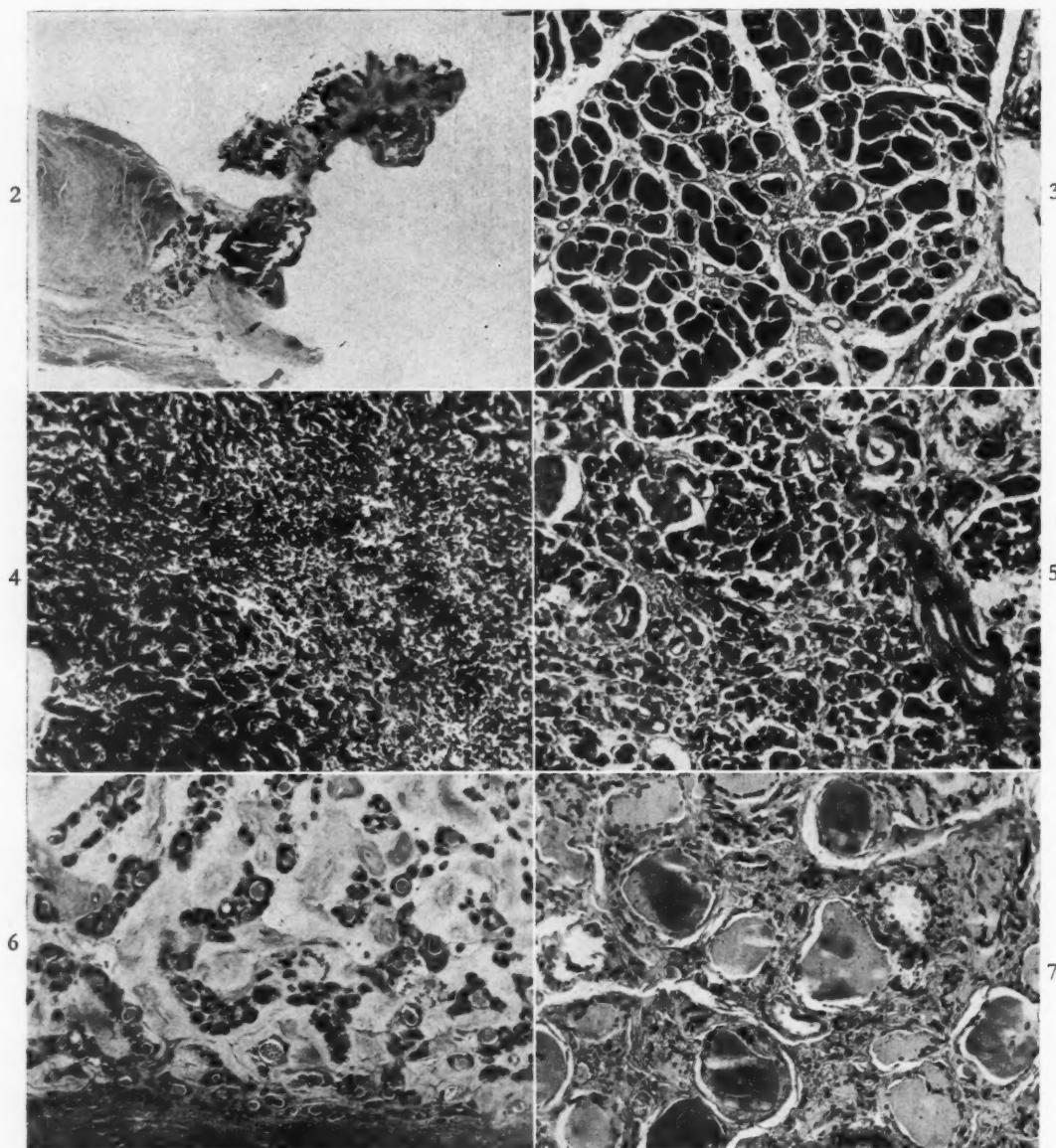


FIG. 2. Total section through the base of the left ventricle and the deformed, calcified cusp of the aortic valve.

FIG. 3. Diffuse interstitial fibrosis in the myocardium.

FIG. 4. Central atrophy of the hepatic cells with increased fibrous tissue about the central veins and adjacent sinusoids.

FIG. 5. Interstitial fibrosis and separation of the acini in the pancreas with a resulting lobulated appearance typical of chronic passive congestion.

FIG. 6. Microfollicles and degenerated stroma at the edge of the adenomatous nodule in the thyroid.

FIG. 7. Interstitial fibrosis in the thyroid. Note the absence of hyperplastic changes in the epithelium of the acini.

aortic valve, more in the right anterior cusp than in the others and a defect in the posterior cusp measuring 5 by 6 mm. in diameter. The absence of arteriosclerosis in the aorta was worthy of note. Figure 2 is a section of the base of the left ventricle and the aortic lesion; it is apparent that the disease is entirely healed, whatever it may

have been. There is nothing but fibrous tissue and large masses of calcium throughout the valve and in the valve ring. In Figure 3 a section of the myocardium is seen in which there is slight fibrosis throughout the interstitial tissue. The next photograph (Fig. 4) is of a section of the liver in which the hepatic cells of the central portions of

the lobules have atrophied and been replaced by an increased amount of connective tissue about the central vein and sinusoids. This finding indicates that the patient had chronic passive congestion of the liver for some period of time with consequent development of congestive cirrhosis. Figure 5 is a section from the pancreas in which there is interstitial fibrosis and accentuation of the lobular character, changes which again are a manifestation of chronic passive congestion of long-standing.

In Figure 6 is a portion of the nodule in the right lobe of the thyroid in which there were numerous small acini, containing in some areas a small amount of colloid embedded in acellular, homogeneous material, changes typical of degeneration of a thyroid adenoma. The remainder of the thyroid (Fig. 7) is not involved by the adenomatous process; the acini are of variable size, filled with rather dense homogeneous colloid. The epithelial cells are of a cuboidal or even flattened character. In between the acini there is considerable increase in the fibrous connective tissue. The last photograph (Fig. 8) is of a section from the lung taken from an area adjacent to an infarct; fluid and a few cells are present in all the alveoli. Cultures of this part of the lung revealed no growth and stains for bacteria show none in these sections. Whatever organisms produced the pneumonia had therefore been destroyed by the time the patient died.

Review of these pathologic findings enables certain interpretations, which are relative to many of the questions raised during the clinical discussion, to be made. First, the cusps of the aortic valve were deformed and unequal but did not resemble a typical bicuspid valve of the congenital type although they did produce both aortic stenosis and insufficiency. The insufficiency was probably on the basis of the defect of the posterior cusp which was of considerable magnitude. There was no disease of the mitral valve, but there was arteriolar disease and that had led to the loss of myocardial tissue and interstitial fibrosis throughout.

The question of whether or not the pa-

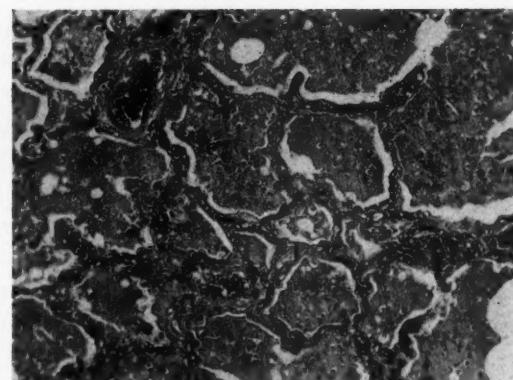


FIG. 8. Edema fluid and slight cellular exudate in the alveoli of the lung indicative of both edema and bronchopneumonia.

tient had thyrotoxicosis certainly cannot be answered definitively on the basis of histologic examination. However, one is justified in stating that there is less than a 50 per cent chance that this thyroid was toxic. The latter statement is based on the fact that in most instances toxicity of the thyroid is associated with hypertrophy and hyperplasia of the epithelial cells although not invariably so. There are other reasons against this gland having been hyperactive in the recent past. For example, the remainder of thyroid tissue other than the adenoma represents a so-called "burnt out" thyroid such as might result from hyperthyroidism at an earlier date. Second, one might have expected to find cirrhosis of the liver of some magnitude. Such was not the case. Cirrhosis is found in association with a significant number of cases of hyperthyroidism. It is probable that some of the interstitial fibrosis in this gland resulted from the radiation used in therapy.

There were infarcts and bronchopneumonia in the lower lobe of the right lung which undoubtedly contributed to the terminal clinical episodes. There is no anatomic explanation of the psychosis; the brain was both grossly and microscopically normal to ordinary examination and probably would be to special examination as there are no significantly constant morphologic changes in the brain in psychoses of this type.

If one rigidly applies the usual criteria

for identification of rheumatic endocarditis and arteriosclerosis of the aortic valve, he finds it necessary to postulate both diseases were present here because both the substance and the base of the cusps are involved. Personally, I would prefer to accept this case as probably rheumatic in origin but with the same reservations as were expressed clinically. Despite the absence of a definite history of rheumatic fever it is quite likely that this lesion was rheumatic. The absence of arteriosclerosis in the aorta would, I think, be against a diagnosis of the Mönckeberg type of calcific aortic stenosis.

DR. WOOD: The location and superficial appearance of the large lesions on the aortic valves remind one of the vegetations of bacterial endocarditis. Dr. Moore, do you consider it possible they might represent healed, calcified vegetations?

DR. MOORE: I was not going to bring that up because I have no definitive proof for my own belief that all cases of calcific aortic stenosis represent healed bacterial endocarditis. There is excellent authoritative opinion that rheumatic endocarditis alone can result in this type of calcification and distortion of the valve. The usual

rheumatic valvulitis, however, does not result in such destruction and calcification in the affected tissue, so I believe there must be some additional factor responsible for that type of reaction which is not present in ordinary cases of that disease. Since both destruction of the valve and calcified masses in older vegetations are recognized features of proven bacterial endocarditis, the postulate that the disease is the underlying process in the development of calcific aortic stenosis appears reasonable.

Anatomic Diagnoses: Chronic endocarditis of the aortic valve with nodular calcification of the coronary cusps and defect in the posterior cusp; healed infarct of the left ventricle and intraventricular septum at the apex of the heart; focal fibrosis of the myocardium; partially organized thrombi in the apices of the right and left ventricles; passive congestion of the lungs, liver, spleen and pancreas with fibrosis of the liver; partially depigmented and recent infarcts of the lower lobes of the right lung with bronchopneumonia; solitary adenomatous nodule in the right lobe of the thyroid; fibrosis of the thyroid without evidence of hyperplasia.

Special Feature

The Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE THIRD ANNUAL MEETING, NEW ORLEANS,
JANUARY 29, 1949

PROCEEDINGS

(Read by Presentation)

OBSERVATIONS ON TWO NEWER HEMOPOIETIC VITAMINS—VITAMIN B₁₂ AND ANIMAL PROTEIN FACTOR. *William J. Darby, M.D. and (by invitation) Edgar Jones, M.D.* From The Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tenn.

Patients with anemias associated with megaloblastic arrest respond hemopoietically to four types of nutritional factors or metabolic products: the pteroylglutamates, vitamin B₁₂, microbial animal protein factor (APF) and thymine. Three of these are available in crystalline form; the fourth (APF) is not but may be quantitated by chick growth studies.

We have made observations on the responses to crystalline B₁₂ (administered parenterally) in eleven patients with pernicious anemia, nutritional macrocytic anemia or sprue. These studies have included evaluations of the minimal effective dosage for induction of hemopoietic and clinical remissions and for maintenance of the patient. These observations to date indicate the approximate equivalence of 1 microgram of crystalline B₁₂ to 1 USP unit of antiperneous anemia liver extract.

In pernicious anemia the remissions produced by B₁₂ therapy have been characterized by relief of glossitis, an increased sense of well being, initial hemopoietic response typical of an adequately treated anemia patient, maturation of the megaloblastic marrow, weight gain, decrease in fecal urobilinogen and, in two patients, disappearance of early neurologic symptoms. In two cases of sprue the results have been less clearly defined and our experience indicates a greater quantitative requirement in this syndrome. Nutritional macrocytic anemia has responded in a manner comparable to pernicious anemia. Evidence will be presented indicating an approximate correspondence of

activity of APF in pernicious anemia (parenteral administration) and in the chick.

Since these two factors are effective parenterally it does not appear that they correspond to Castle's extrinsic factor although their association with animal protein would imply that they may.

CLINICAL AND LABORATORY RESIDUALS IN PATIENTS TREATED FOR SPRUE. *Herbert J. Fox, M.D. (Introduced by Eugene A. Stead, Jr., M.D.)* From Duke University School of Medicine, Durham, N. C.

A follow-up clinical and laboratory study was made on twenty patients previously diagnosed as having sprue who had had from five to fourteen years of nutritional rehabilitation and specific therapy. Each had had a chronic illness characterized by loss of weight, anemia, glossitis, diarrhea, meteorism and steatorrhea.

This study was undertaken to determine the residual disability and laboratory evidence of absorptive defects in sprue that persisted despite prolonged therapy. Nine of the twenty patients had not achieved full rehabilitation, had remained underweight, deficient in strength and had periodic recurrences of diarrhea and glossitis. Physical activity was restricted. Dietary fat was tolerated poorly. Continued liver therapy was necessary. A five-day fat balance test showed a sub-normal absorption of dietary fat in all nine patients. Their stools, by a measured fecal output over three-day periods, were increased in bulk. Mild anemia with a tendency toward macrocytosis was present. Unemulsified vitamin A showed flat absorption curves in contrast to normal curves with emulsified material. Roentgenologic study of the small intestine showed coarse irregularities and segmentation alternating with dilatation. The effect of folic acid on fat absorption was observed in seven of these nine patients. Although they had received maintenance doses of folic acid, 15 to 30 mg. daily for six months or longer and had

bowel habit improvements not seen in liver therapy, still all seven showed steatorrhea.

Eleven of the twenty had not received specific therapy for several years and were apparently fully recovered, showing none of the clinical or laboratory residuals seen in the other nine patients.

The sprue syndrome apparently represents a temporary motor and absorptive abnormality of the intestines from nutritional deficiency, or a more permanent disease which persists in spite of nutritional rehabilitation and therapy. The latter may be congenital or represent a sequela of inflammatory or other damage to the gut wall.

CHANGES IN ELECTROPHORETIC PATTERNS OF SERA IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH URETHANE. *Edith S. Dillon, M.D. (by invitation), M. L. Dillon, M.D. (by invitation) and R. W. Rundles, M.D.* From Duke University School of Medicine, Durham, N. C.

In six patients with multiple myeloma treated with urethane, fever and bone pain at rest and during activity subsided and anemia, hyperglobulinemia and proteinuria were ameliorated or corrected. Abnormal plasma cells in the bone marrow became altered in appearance and decreased in number or disappeared from the marrow. After six to eight months there was x-ray evidence of recalcification of bone.

Electrophoretic studies on sera of four of these patients showed conspicuous reduction in the amount of abnormal serum globulin after urethane therapy. In one patient globulin with gamma mobility comprised 45.7 per cent of the total serum protein before treatment. A total dosage of 240 Gm. of urethane was given orally over a period of two months. Five months after completion of therapy the gamma globulin component was 23.8 per cent and at nine months it was 22.9 per cent. In a second patient with 49 per cent gamma globulin before treatment there was a fall to 18 per cent in four months and 19.1 per cent at seven months. In a third patient "M" globulin comprised 45.2 per cent of the serum protein before treatment and 33.4 per cent three and one-half months later. The abnormal globulin rose again to 40.6 per cent accompanied by a decline in hemoglobin, red count and hematocrit and the reappearance of over 20 Gm. per day of Bence-Jones protein

in the urine. A fourth patient excreting about 25 Gm. of Bence-Jones protein daily in the urine had a normal percentage distribution of serum protein components before therapy. After two months of urethane the gamma globulin fell from 10.5 per cent to 8.5 per cent with a 75 per cent reduction in the amount of Bence-Jones protein in the urine.

ACTIVATION OF SERUM PROTEOLYTIC ENZYME. *Jessica H. Lewis, M.D. (by invitation) and John H. Ferguson, M.D.* From The Department of Physiology, University of North Carolina, Chapel Hill, N. C.

Normal blood contains a powerful proteolytic enzyme system which, if fully activated, is capable of destroying all the fibrinogen and probably much of the other plasma protein in a few minutes. Serum contains enzyme precursor (proenzyme) and enzyme inhibitor (anti-enzyme). *In vivo* activation occurs only under certain rare pathologic conditions.

We have set up systems for study of the activation of this proenzyme *in vitro*, using various "activators" including chloroform, streptokinase and staphylokinase. Proteolytic activity is measured by the rate of lysis of a standard fibrin clot.

Proenzyme is prepared from (1) human, (2) canine (3) bovine serum by 25 per cent alcohol fractionation at 0°C. This fraction contains almost all the proenzyme and a reduced amount of anti-enzyme. Spontaneous activation of these preparations did not occur.

Chloroform treatment of the proenzyme preparations causes further marked reduction of the antifibrinolytic activity of these fractions. Fibrinolytic activity appears in these preparations only slowly and rarely to maximal amounts. It is concluded that the main action of chloroform is to remove enzyme inhibitors and to allow either spontaneous activation or activation by substances already present in the serum fractions. Streptokinase readily activates human proenzyme but does not affect dog or bovine preparations. In optimal amounts its effect is immediate but in suboptimal amounts a period of preliminary incubation with proenzyme is necessary for maximal fibrinolytic activity. Staphylokinase activates both human and dog proenzyme but does not affect bovine material. The kinetics of the staphylokinase reaction also

differ from streptokinase in that even in optimal amounts staphylokinase reacts relatively slowly, the rate being dependent upon the temperature. Streptokinase and staphylokinase are relatively heat stable, as is the proenzyme, while the activated enzyme is markedly heat labile.

In conclusion, the applicability of these facts to the measurement of human and dog proenzyme is presented.

THERAPEUTIC USE OF RADIOACTIVE GOLD IN MALIGNANT DISEASE. *P. F. Hahn, M.D.*
From The Cancer Research Laboratories, Meharry Medical College, Nashville, Tenn.

Radioactive gold¹⁹⁸ is produced by a neutron-gamma reaction in the chain reacting pile from the 100 per cent naturally occurring gold.¹⁹⁷ Therefore, there are no undesirable side reactions or contaminant isotopes produced. Gold¹⁹⁸ lends itself readily, when in the colloidal state, to administration by vein in the treatment of diseases of the lymphoid-macrophage system. It is also useful in the treatment of discrete tumor masses by direct infiltration as the colloid. The half-life (2.7 days) is sufficiently long for the isotope to perform its required work, i.e., delivering radiation over an integrated period of slightly over a week rather than in a short burst. Its life is not so long but that one is able to "titrate" the ionizing radiation in the patient and certainly not long enough to act as a carcinogenic agent in itself. Its biologic behavior is comparatively well understood and, as the colloid of the metallic element, is not susceptible to solution by tissue fluids. The chemical behavior of the element is well known. To date it has been found that once this material is delivered underneath the skin the tissue tolerance for radiation is several times what was anticipated. It is non-toxic. Its administration does not give rise to radiation sickness. The cross section to thermal neutrons ranges from 100 to 200 times that of most isotopes. The degree of dispersal of the gold colloid is very high, the particle size being of the order of magnitude of 60 milli-micra, there being approximately 3 trillion particles per cc. of colloid suspension. Each of these acts as a near-point beta emitter. The mean free path of the beta particle in the tissue is of the order of 3.8 mm. Thus adjacent structures and tissues are relatively unaffected in contrast to the radiation produced by use of radium needles and

radon seeds. Thus with gold colloid the beta radiation is used to its fullest extent and the gamma is relatively negligible, constituting approximately 10 per cent of the total ionization response obtained.

The chief obstacle to widespread use of this material in the treatment of malignant tumors at the present time is lack of knowledge of the beta ray tolerance of various tissues. It is also difficult on many occasions to estimate the volume of tissue subjected to infiltration and therefore we are occasionally unable properly to estimate the equivalent roentgen dosage delivered to such tissues. Radio-autography is being employed in an attempt to study the degree to which this material is diffused in the tissue infiltrated. Also certain spreading agents are being investigated as to their capacities to modify such diffuse localization of the isotope. This isotope promises to be very useful in the future treatment of neoplasms.

TREATMENT OF VARIOUS INFECTIONS WITH PROCaine PENICILLIN IN OIL WITH 2 PER CENT ALUMINUM MONOSTEARATE. *Harold L. Hirsh, M.D. and Walter Kurland, M.D.* (Introduced by Hugh S. Hussey, M.D.). From The Georgetown University Medical Division, Gallinger Municipal Hospital and the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

Adequate preparations of procaine penicillin in oil with 2 per cent w/v aluminum monostearate give therapeutically effective blood concentrations for at least ninety-six hours and generally for one hundred twenty hours. Significant blood concentrations have been found within one hour after injection.

Our previous experience has demonstrated that penicillin therapy for about five days is generally sufficient in the treatment of any acute infection. The present study was undertaken for the purpose of determining whether infections caused by organisms such as the pneumococcus and streptococcus could be adequately treated by a single 1 cc. dose of procaine penicillin in oil with 2 per cent w/v aluminum monostearate containing 300,000 units of procaine penicillin.

Twenty-five patients with scarlet fever are included in this series. A prompt response was noted in all patients. The duration of fever after therapy was started averaged thirty-eight hours.

Streptococci disappeared within forty-eight hours from the throats of all patients from whom positive cultures were obtained before therapy was started. One patient had a recurrence of the hemolytic streptococcus on the fourth day which persisted until another injection of procaine penicillin in oil with aluminum monostearate was given on the eleventh day. Another patient developed purulent otitis media on the tenth day which responded to therapy with aqueous penicillin. Still another patient developed serous meningitis on the seventh day and a fourth, evidence suggestive of acute rheumatic fever on the eleventh day.

Sixteen patients with lobar pneumonia diagnosed on the basis of history and physical findings, serial roentgenograms and/or laboratory studies have been treated with a single injection of the preparation. In all patients the response was prompt and the temperature fell below 100°c. within twenty-four hours. Convalescence was uneventful in all patients.

One patient with streptococcal pharyngitis was treated in an identical manner and made an uneventful recovery.

Three patients with cellulitis were given two injections (300,000 units each) at five-day intervals with complete resolution of the involved area.

The results in this series of patients are comparable to those seen in patients treated with other established penicillin regimens.

EFFECT OF DIHYDROERGOCORNINE ON THE PULMONARY RESPONSE TO HISTAMINE AND METHACHOLINE IN SUBJECTS WITH BRONCHIAL ASTHMA. *John J. Curry, M.D., Job E. Fuchs, M.D. and Samuel E. Leard, M.D.* (Introduced by Harold Jeghers, M.D.) From The Robert Dawson Evans Memorial, Massachusetts Memorial Hospital and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

It has been reported that interruption of the sympathetic nervous system in the lung brings about cessation of asthmatic attacks in certain individuals. Presumably the operation is effective because it prevents noxious stimuli arising within the lung structure from ascending to the cranial centers and producing reflex bronchoconstriction. In a few subjects with bronchial

asthma we have been able to demonstrate that procaine block of the sympathetic pathways of the lung reduces the pulmonary response to injected histamine and methacholine. This is of great interest in view of recently reported studies on the relationship between the degree of asthma and the pulmonary response to these drugs.

In the present communication the effect of a new sympatholytic agent, dihydroergocornine, on the pulmonary response to histamine and methacholine is reported. The method of study has been outlined in detail in previous reports. In brief, an evanescent asthma-like attack is induced by histamine or methacholine and the subsequent reduction in vital capacity and maximum ventilation is measured. Dihydroergocornine is then administered and the injection of histamine or methacholine repeated. The degree of protection is thus easily ascertained by objective measurement. The results indicate that in some cases the sympatholytic agent furnishes remarkable protection against the pulmonary reaction to histamine and methacholine. These studies present interesting clinical implications and in addition may furnish further understanding of the fundamental pathologic physiology of the lung in bronchial asthma.

STUDY OF COMPLETE PARENTERAL ALIMENTATION IN DOGS. *H. C. Meng, M.D. (Introduced by William J. Darby, M.D.)* From The Department of Physiology, Vanderbilt University School of Medicine, Nashville, Tenn.

Previous work has led to the development of a stable, fine fat emulsion which was used in an attempt to supply all necessary nutrients to dogs intravenously. The animals were apparently in good health after ten weeks of injections. However, they did show intermittent hematuria and some anemia. It was thought that the hematuria and anemia might have been due to the mechanical difficulties in voiding. The present study was undertaken in an attempt to avoid the previous difficulties and demonstrate the possibility of keeping animals completely healthy by complete parenteral feeding.

In the control period two adult male dogs were fed a complete basal diet which furnished 80 calories per Kg. of body weight per day of which 50 per cent came from carbohydrate,

16 per cent from protein and 34 per cent from fat. Immediately following this period they were given a diet containing the same amount of carbohydrate, protein and fat, but it was infused exclusively by vein. Water was allowed by mouth *ad libitum*, and liver extract and folic acid were given intramuscularly every week. Protein was furnished in the form of the casein hydrolysate, amigen. The fat emulsion contained 10 per cent olive oil which was stabilized with 0.5 per cent span 20, 0.4 per cent asolectin and 0.1 per cent sodium cholate. It was homogenized in a high pressure viscolizer. Vitamins A, D and E were incorporated in the emulsion. The dogs were infused daily for four weeks and then sacrificed.

There was never any hematuria or anemia and the animals remained healthy, lively and in good spirits throughout. Extensive laboratory tests were performed during the experimental period, and the outstanding feature of all of them was their constancy. The nitrogen balance was negative during the first week but was subsequently positive. There was a slight gain in body weight. Histopathologic study of the organs of the animals showed them to be entirely normal. It is concluded that this fat emulsion is non-toxic and that the body is capable of utilizing fat in this form.

GASTROMETRIC STUDIES BEFORE AND AFTER VAGOTOMY. *E. J. Linberg, M.D. (by invitation), K. S. Grimson, M.D. and (by invitation) J. R. Chittum, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Gastrometric examinations of the fasting stomach have been made before vagotomy in thirty-eight patients with peptic ulcer and at intervals afterward in fifty-six. Eleven were studied twenty-four to thirty-seven months after operation. The usual method employed intragastric balloons inflated at intervals of five to fifteen minutes using increments of 50 cc. of air to a total volume of 300 cc. Intragastric pressure was recorded continuously using a bromoform manometer. Resting intragastric pressure as judged by the tone base line was moderately increased after vagotomy. Strong fluctuations of intragastric pressure above this tone base line ceased or were markedly reduced. Stretch reflexes occasionally occurring during inflation of the balloon before vagotomy were not ob-

served afterward. Tonus contractions occurred occasionally before and after operation. Effects persisted, there being no evidence of recovery during periods of observation as long as three years.

Effects of overdistention of the stomach were studied. Three patients were tested before vagotomy and one or two weeks afterward by increasing the balloon volume to 1,000 cc. Resting tone increased with greater distention before and after vagotomy, the increase afterward being greater. Increase of contraction waves with higher volumes did not occur in patients tested during the first several weeks after vagotomy. Fifteen patients were tested twelve to thirty-eight months after vagotomy using volumes up to 1,000 cc. Increased height of the tone base line occurred, that at 1,000 cc. being double that at 300. Some patients had low contraction waves at a 300 cc. volume. These increased in height with greater distention.

Comparison of gastrometric records of motility with standard insulin tests reveals changes of motility to be more consistent, a normal pattern appearing after operation only in one patient definitely known to have an incomplete vagotomy.

MECHANISM OF REMOVAL OF SULFONATED DYES FROM BLOOD PLASMA BY MAMMALIAN LIVER. *Ralph W. Brauer, M.D. (Introduced by John Adriani, M.D.)* From The Department of Pharmacology and Experimental Therapeutics, Louisiana State University School of Medicine, New Orleans, La.

It will be shown that three factors are involved in the excretion of sulfonated phthalein dyes, especially sodium phenoltetrabromphthalein sulfonate by the liver: circulation of blood through the liver, uptake of the dye from the blood plasma by the hepatic parenchyma and reexcretion of the dye store in the hepatic cells in the bile. Data will be presented in particular with regard to the second mechanism which has been investigated by means of liver perfusion studies as well as by *in vitro* studies of liver slices. The uptake mechanism appears to be independent of metabolic processes which can be poisoned by either cyanide, fluoride or mercuric ion, and it does not appear to be interfered with by administration of India ink or of carbon tetrachloride prior to the experiment under condi-

tions which lead to a marked decrease of the BSP clearance in the intact animal. The evidence to be presented supports the concept of the liver functioning as a multiple unit extraction system in which successive units function at decreasing BSP concentrations. This concept is derived in part from the much greater efficiency of the perfused liver compared to incubated liver slices in removing BSP from the solutions with which they are brought in contact. The tendency of BSP to form little dissociated complexes with various proteins is proposed as the basis of the driving force governing the flow of dye from plasma or perfusion solutions into the liver cells. Data to be presented with regard to the other two factors just mentioned will include studies of the relative concentrations of BSP in blood plasma and liver lymph of normal and carbon tetrachloride-poisoned or India ink-injected dogs as well as preliminary data obtained by the use of BSP containing radioactive sulfur in the sulfonic acid radical of the molecule.

THERMAL SEPARATION OF RADIOMERCURY FROM RADIOSODIUM. *P. B. Reaser, M.D. (by invitation), G. E. Burch, M.D. and (by invitation) S. A. Threepoint, M.D. and C. T. Ray, M.D.* From The Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana, New Orleans, La.

A number of physiologic phenomena can be studied best by the simultaneous administration of two or more radioactive isotopes. This report is concerned with the description of a method which is practical in separating radioactive mercury from radioactive sodium (Na^{22}) and presumably from other elements with similar thermodynamic constants. Its organic combinations are characterized by instability. If they are decomposed, the consequent behavior of the Hg can be used to advantage.

To study the pharmacodynamics of diureses produced by a mercurial diuretic it is desirable to use such a compound synthesized with radio-mercury ($Hg^{203-205}$). This isotope of mercury has a physical half-life of 51.5 days. Its "practical" half-life was found to vary considerably, depending on environmental and chemical conditions.

Thirty samples of radioactive mercurhydrin and radioactive sodium (Na^{22}) were allowed to dry at room temperature. Thirty samples of a solution of radioactive sodium (Na^{22}) chloride

were prepared, to which, after drying, were added known amounts of radioactive mercurhydrin solution. After being counted all preparations were heated in an oven to 250°c. for one hour and twenty minutes. Upon removal and cooling they were again counted.

A mean of more than 99 per cent of the mercury of a mercurhydrin preparation was driven off by heat, whereas under identical conditions a sodium preparation did not change significantly. Naturally, stable mercurial salts or compounds would have to be rendered labile to heat to take advantage of vapor tension and boiling point differences.

SPECTROPHOTOMETRIC DETERMINATION OF BLOOD OXYGEN. *J. B. Hickam, M.D. and K. R. Frayser, M.D. (Introduced by Eugene A. Stead, Jr., M.D.)* From The Department of Medicine, Duke University School of Medicine, Durham, N. C.

Determination of blood oxygen content by gasometric methods is time-consuming, thus limiting the number of observations made in a single study. In many cases it is the arteriovenous difference across lung, liver, kidney or brain which is particularly desired. The present abstract reports the development of a rapid, accurate spectrophotometric method for determining the difference in oxygen content between two samples and for estimating with fair accuracy the absolute oxygen content of the individual samples.

The Beckman spectrophotometer equipped with standard 0.5 cm. cuvettes was used. Measurements were made at 660 μ . At this wave length the absorption coefficient of reduced hemoglobin is approximately five times that of oxyhemoglobin. The method operates on the principle that the difference in optical density between two samples of blood from the same subject having the same hemoglobin content is proportional to their difference in oxygen content. In practice the more highly oxygenated sample is used as the blank against which the other sample is read, thus eliminating the effect of "inactive" hemoglobin and other substances which do not alter their optical density with a change in oxygen tension. Samples are hemolyzed by a concentrated saponin solution before reading. Fifty-six gasometrically controlled determinations of A-V difference ranging from 0.5 to 15.0 volumes per cent have been made on

blood from nine different subjects. The standard deviation from regression is 0.23 volumes per cent. Estimate of the absolute oxygen content of a sample can be made by the additional colorimetric determination of the total hemoglobin. Satisfactory allowance can be made for a change in the hemoglobin concentration during the course of a study. In routine use the method is quite simple and has proved to be five to six times faster than the ordinary gasometric technic. The accuracy appears to be roughly equivalent to that of gasometric methods.

COMPARISON OF RESULTS OF MEASUREMENT OF RED BLOOD CELL VOLUME BY DIRECT AND INDIRECT TECHNIQUES. *William Parson, M.D., H. S. Mayerson, M.D., Champ Lyons, M.D., R. T. Nieset, M.D. (by invitation) and W. J. Trautman, Jr., M.D. (by invitation).* From The Departments of Medicine, Physiology and Surgery and the Laboratory of Biophysics, School of Medicine, Tulane University and the Alton Ochsner Medical Foundation, New Orleans, La.

Concomitant measurements of red blood cell volume and plasma volume were made with the radioactive phosphorus (P-32) technic and with the T-1824 method respectively in ten normal and thirty-five hospitalized individuals. A standard correction factor of 0.915 was used to correct the hematocrit values for trapped plasma. When this correction is used, the values calculated for red cell volume from the plasma volume and hematocrit data agree well with the values obtained by direct measurement of the red cell volume with the P-32 method. Total blood volumes calculated from the red cell and hematocrit and from the plasma volume and hematocrit show satisfactory agreement with the total blood volumes as calculated from the sum of the actually determined red cell and plasma volumes. Comparison of the (*in vitro*) peripheral and the body hematocrit also shows good agreement. The data suggest that the whole blood volume can be measured with an average discrepancy of less than 5 per cent by the plasma-dye-hematocrit method provided the corrected hematocrit value is used.

PLASMA VOLUME AND EXTRAVASCULAR THIOCYANATE SPACE IN EXPERIMENTAL SERUM

AUGUST, 1949

SICKNESS IN RABBITS. *George T. Harrell, M.D. and (by invitation) Ernest H. Yount, M.D.* From The Department of Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

Patients with Rocky Mountain spotted fever develop clinical edema during the acute phase of the disease. Frequently the plasma volume is reduced transiently and peripheral circulatory failure may ensue. The maximum changes usually occur just before the temperature begins to fall. The time relationships suggest the possibility that an antigen-antibody reaction may explain the pathogenesis of the alteration in capillary permeability. To test this thesis twelve rabbits were injected intravenously with 5 cc. Kg. of human plasma. The plasma volume was measured by the Evans blue technic and the thiocyanate space simultaneously determined by the loss of thiocyanate from the plasma. Three base line determinations were made before injection; three additional determinations were made on successive days, beginning with the appearance of precipitins for human plasma in the rabbit's blood, usually on the seventh or eighth day after injection. A final determination was done one week later. A significant rise in the thiocyanate space was observed and was accompanied by clinical manifestations of serum sickness—edema, fever and listlessness. The drop in the plasma volume was small but was statistically significant for the group. The changes reverted to normal in convalescence. Similar results were obtained in a second group after the injection of purified human serum albumin.

STUDIES ON THE HEPATIC CIRCULATION IN HYPERTHYROIDISM. *J. D. Myers, M.D. (Introduced by Eugene A. Stead, Jr., M.D.)* From The Duke University School of Medicine, Durham, N. C.

A group of patients with clinically typical hyperthyroidism have been investigated in the fasting state in regard to total cardiac output, hepatic blood flow and splanchnic oxygen consumption. These measurements were made by the technic of venous catheterization. The data obtained were compared with a set of control data on subjects without significant disease.

The mean figures on eleven patients with

hyperthyroidism were as follows: metabolic rate, 54 per cent; cardiac index, 5.0; hepatic blood flow (BSP method), 920 ml. per minute per square meter of body surface; mixed arterio-venous oxygen difference, 4.4 volumes per cent; hepatic A-V oxygen difference, 6.8 volumes per cent and splanchnic oxygen consumption, 61 ml. per minute per square meter. Corresponding figures in twenty-seven control subjects were: cardiac index, 3.8; hepatic blood flow, 870; mixed A-V oxygen difference, 4.0; hepatic A-V oxygen difference, 4.3 and splanchnic oxygen consumption, 37. The splanchnic oxygen consumption in the controls comprised 23 per cent of the total oxygen consumption; in hyperthyroidism the corresponding figure was 30 per cent.

In summary, the patients with hyperthyroidism showed a moderate elevation in cardiac output without concomitant increase in hepatic blood flow. At the same time their splanchnic oxygen consumption was increased in proportion to the elevation in total metabolism. These circumstances require in hyperthyroidism an increase in oxygen extraction in the splanchnic area. This situation of an increased hepatic A-V oxygen difference in the fasting state is the same as that found in heart failure and may well play a significant role in the frequency of hepatic disease in thyrotoxicosis.

SOME FACTORS INFLUENCING SODIUM EXCRETION. *Jerry M. Lewis, M.D. and S. Maple Sevier, M.D. (Introduced by Tinsley R. Harrison, M.D.)* From The Department of Internal Medicine, Southwestern Medical College, Dallas, Tex.

The hourly urinary excretion of sodium has been studied in normal subjects under conditions of constant intake of water and sodium. Change from the recumbent to the sitting posture is accompanied by a sharp decline in sodium excretion. The usual duration of the lag period of this phenomenon suggests a chemical rather than a nervous mechanism. In the subjects thus far studied compression of the neck by a blood pressure cuff inflated to 25 mm. in a subject in the sitting position caused an increase in sodium excretion over that in a patient in the same position without the cuff.

The results taken together appear to indicate that: (1) some type of central mechanism may be a factor in regulation of sodium excretion and (2) the nature of this mechanism is still uncertain but it does not appear to be related to

alterations in cardiac output or in cerebral blood flow.

CHLORIDE BALANCE IN CONGESTIVE CIRCULATORY FAILURE. *Henry A. Schroeder, M.D.* From The Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

Forty patients suffering from congestive circulatory failure of cardiac origin were studied on a metabolic service for long periods of time. The intake of salt, calories and fluids was constant for varying intervals. The urinary output of chlorides was measured daily, over 2,200 determinations being made. Various procedures which alter the course of congestive failure were instituted after adequate control periods. (1) The amount of chlorides excreted in the urine was either depressed or was elevated very slightly when the intake of salt was increased, either by ingestion or by intravenous injection of a hypertonic solution. (2) Restriction of the fluid intake usually resulted in retention of chlorides and elevation of the intake sometimes initiated a chloride diuresis. (3) When the theoretical weight loss was calculated from the total urinary excretion of chlorides over several weeks and compared to the actual loss of weight, there was good agreement in about one-half the cases; in the other half there was an indication that the patients had been in a state of overhydration. Therefore, disturbances of both salt and water balance, separately and together, were present in cases of congestive failure. (4) Of the effects of diuretic agents, theocalcins was found to influence principally the excretion of water and the mercurial diuretics, the excretion of chlorides. Digitalis appeared to affect both but acted in only one-third of the patients. (5) Severe overhydration occurred in eighteen patients; this was accompanied by oliguria and dilution of plasma electrolytes. When electrolyte levels were elevated by intravenous injection of hypertonic saline, diuresis often became established. In these cases renal failure appeared to result from loss of extracellular sodium chloride. (6) When the urinary concentration of chlorides was considered in the light of other functions of the kidney, it appeared that the amount excreted was too low to be accounted for by diminution of renal blood flow and that extrarenal factors, presumably from the adrenal cortex and pituitary, were possibly operating.

MECHANISMS OF SALT AND WATER RETENTION IN HEART FAILURE. *D. J. Highes, M.D. (by invitation), H. H. Turner, M.D. (by invitation), A. J. Moseley, M.D. (by invitation) and A. J. Merrill, M.D.* From The Emory University School of Medicine, Atlanta, Ga.

Much dissatisfaction has been expressed at the idea that retention of salt and water in heart failure is caused solely by the low renal filtration rate. The only explanation available for the fact that the tubules reabsorbed a larger proportion of the filtered sodium was their "fundamental sodium-conserving function." Many investigators have suspected an adrenal cortical effect as the reason. Conn's recent discovery of the inverse relationship between the sweat sodium concentration and activity of the sodium-retaining hormone of the adrenal cortex offered an excellent method of determining the activity of this hormone in heart failure. Four patients with cardiac failure were found to have low sweat sodium concentrations falling within the range of Cushing's disease. Three had a very low filtration rate and all had severe intractable failure. One had a normal filtration rate but he also had severe failure. Ten patients had a normal or high sweat sodium concentration. In two the renal plasma flow and filtration rate were not measured. In all but one of the remaining the filtration rate was either normal or only slightly reduced, the renal plasma flow was only moderately diminished and failure was much more easily controlled although twenty-four-hour sodium excretion was low on a 200 mg. sodium diet. The remaining patient had a very low filtration rate despite the fact that the renal plasma flow was well above the level at which the filtration rate was reduced. It was believed that he probably had had glomerulonephritis with perhaps a thickened Bowman's capsule. The fact that he retained sodium despite a normal sweat sodium suggests that reduced filtration played a part in the sodium retention. We have one other patient with a slight reduction in the renal plasma flow and filtration rate of 49 cc. per minute with intractable chronic heart failure. Her sodium retention was thought to be on a basis similar to that of the patient just mentioned. If patients with severe heart failure and edema are relieved of as much edema as possible with the

aid of mercurial diuretics, a fall in blood sodium concentration occurs sometimes to a level as low as 114 mEq. (normal 136 to 143). Despite this fall the patient does not lose his edema. While this could be due to an artificial imbalance between the proximal and distal convoluted tubules, it could mean that the posterior pituitary antidiuretic hormone is operating.

The exact time relationships between these phenomena in the course of heart failure is uncertain. Perhaps further work will clarify this.

INTRAVENOUS CATHETERIZATION OF THE HEART IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE. *Don W. Chapman, M.D. and Lloyd Gugle, M.D. (Introduced by James A. Greene, M.D.)* From The Baylor University College of Medicine, Houston, Tex.

Recent advances in surgical alteration or correction of certain congenital defects of the heart and great vessels make it imperative that a more accurate diagnosis of such lesions be made. Intravenous catheterization of the heart has been a useful aid to ascertain the condition in patients suspected of having such congenital abnormalities.

A 6 French or 9 French special catheter is introduced into the median basilic vein and passed under fluoroscopic control via the subclavian vein and superior vena cava into the right side of the heart and into the pulmonary artery and its branches. The oxygen content of samples of blood are obtained at various sites and should not differ normally by more than 1.9 volumes per cent. Pressures in the various sites are recorded by means of a Hamilton manometer. This procedure has been used in fifty-eight patients with, or suspected of having, congenital defects of the heart or great vessels. The results illustrate its value to ascertain whether or not the patient has a defect, to indicate the operability when defects are discovered and to suggest the prognosis.

In cases of auricular septal defect the oxygen content of the blood from the right atrium is greater than that in the vena cavae. In patients with ventricular septal defects a sufficient increase in oxygen content in the blood from the right ventricle is demonstrated when compared with that in the atrium. Septal defects may also be demonstrated by passing the catheter through the defect into the left side of the heart.

Patent ductus arteriosus is demonstrated by finding an increase in oxygen content of blood from the pulmonary artery as compared with the right ventricle and occasionally by an increased pulmonary arterial pressure. Cases of cyanotic congenital heart disease are presented showing the usual absence of the left to right shunt. Cyanotic patients with increased pressure in the right ventricle or pulmonary artery are discussed. Combined lesions such as cyanotic congenital heart disease with patent ductus arteriosus may be found and patients with such abnormalities are described. Several patients who were suspected of congenital defects but in whom the catheterization studies were normal are described. A case in which a pulmonary vein was found to empty into the right (?) or common (?) atrium is reported. Complications of the procedure, including premature ventricular contractions, phlebitis and venospasm, are described.

DIRECT ARTERIAL PUNCTURE AND PHOTO-ELECTRIC PLETHYSMOGRAPHY IN THE DIAGNOSIS OF COARCTATION OF THE AORTA. *Melvin L. Goldman, M.D. (by invitation) and Henry A. Schroeder, M.D.* From The Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

In thirteen patients with coarctation of the aorta photoelectric plethysmograms were made of the pulses in the ears, toes, fingers and scrota, and the blood pressure in the brachial and femoral arteries was measured with a Hamilton manometer. By these means it was possible to determine roughly the degree of constriction of the aorta. In eleven of the patients femoral diastolic pressures were the same or slightly less than that in the brachial. In the others it was considerably lower. Both groups showed severe constriction of the aorta at operation. Diastolic pressure was elevated in only two; one showed a minimal constriction of the aorta by retrograde aortic arteriography which was reflected by a slightly lower systolic pressure in the femoral artery than in the brachial. The pulse wave velocity was found in all patients but one to be considerably less than normal. Two subjects were studied after surgical correction of the defect; the changes observed were in the direction of normal, the pulse wave velocity returning to normal values.

The mechanism of hypertension in coarctation was investigated by partial constriction of the brachial artery to a point above diastolic pressure by means of a cuff and the blood pressure measured below the constriction. When this was done in normal subjects and in those with coarctation or hypertension, both systolic and diastolic pressures rose significantly above control values, the rise occurring on the next systole. This unusual finding may be the result of the "breaker phenomenon" or may account, in part, for the hypertension observed in these patients.

In the course of these studies four female patients were found to exhibit coarctation, hypogonadism, short stature and shortening of one or more phalangeal, metatarsal or metacarpal bones. The frequency of this combination of findings apparently has not been noted previously.

REVERSAL OF THE LEFT VENTRICULAR STRAIN PATTERN OF THE ELECTROCARDIOGRAM BY ETAMON AND SPINAL ANESTHESIA
Arthur Ruskin, M.D. and Alfred Lane, M.D. (Introduced by Raymond Gregory, M.D.) From The University of Texas Medical Branch, Galveston, Tex.

Hypertensive patients with the left ventricular strain pattern in the electrocardiogram show variability in the latter at different times. This variability has not correlated well with the level of the blood pressure. On the other hand, sympathectomized hypertensive patients have presented, parallel to their relative hypotensive states, favorable changes (toward normal) in the electrocardiogram in about 50 per cent of the cases.

Tetraethyl ammonium, 0.5 Gm. intravenously, usually causes a marked temporary drop in the systolic and diastolic blood pressures of hypertensive patients. Electrocardiograms obtained in the horizontal position at the minimum levels of blood pressure in such cases showed marked elevations of the T waves and frequently of the depressed S-T segments. In other cases showing lesser drops of blood pressure electrocardiograms taken in the sitting posture, with concomitant greater drops in blood pressure, sometimes caused partial reversal of the left ventricular strain pattern.

Spinal anesthesia likewise caused normalization of the electrocardiogram if the blood

pressure fell markedly. No correlation could be established between degrees of drop in blood pressure and the degrees of reversal of the strain pattern. Such electrocardiographic changes could not be obtained following sodium amytaf although the high blood pressure fell, albeit slowly. Etamon lower pressures in non-hypertensive individuals elevated the T waves only in exceptional cases. The possible mechanisms will be discussed at a future date.

ROLE OF THE KIDNEY IN THE PATHOGENESIS OF EXPERIMENTAL HYPERTENSION. *Arthur Grollman, M.D., John Vanatta, M.D. (by invitation) and E. E. Muirhead, M.D.* From The Department of Physiology and Pharmacology, Pathology and Experimental Medicine, Southwestern Medical College, Dallas, Tex.

By application of the artificial kidney to nephrectomized dogs or those in which one ureter was implanted into the small intestine and the contralateral kidney removed it has been possible to determine the role played by the kidney in the pathogenesis of hypertension. In the absence of both kidneys the blood pressure rises gradually, reaching hypertensive levels within the course of a week. If kidney tissue deprived of its excretory function by implantation of the ureter into the gut remains in the body, the animal remains normotensive. These experiments demonstrate the erroneousness of the view that hypertension is the result of the elaboration of a pressor agent (renin, angiotonin, hypertension) by the kidney and prove that the kidney normally performs some incretory function which, when in abeyance, results in the development of hypertension.

EFFECTIVENESS OF SEVERAL ADRENOLYTIC, SYMPATHOLYTIC OR GANGLIONIC BLOCKING DRUGS AGAINST ACUTE AND CHRONIC NEUROGENIC HYPERTENSION. *K. S. Grimson, M.D. and (by invitation) J. R. Chittum, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Priscol, dibenamine and two newer sympatholytic drugs, to be presented as C 7337 and C 5968, and also two ganglionic blocking drugs, etamon and a new product SC 1950, have been tested against increased intracranial pressure

acutely produced in anesthetized dogs and against chronic neurogenic hypertension in dogs.

In increased intracranial pressure experiments dogs under chloralose anesthesia were given progressively larger doses of one test drug intravenously until bilateral occlusion of the carotid arteries no longer significantly increased the blood pressure. Intracranial pressure was then increased by forcing saline through a trochar into the skull. Increase of intracranial pressure in untreated animals stimulated increases of blood pressure to values exceeding 200 mm. Hg. In treated animals the blood pressure gradually decreased during drug administration, occasionally reaching levels below 70 mm. Hg. Increase of intracranial pressure then usually effected only moderate increase of the blood pressure. Two of the six drugs, priscol and C 7337, in occasional experiments completely blocked the pressor response.

Each of the six drugs was also tested in dogs with chronic neurogenic hypertension persisting one to twelve months after excision of the carotid sinuses and division of the depressor nerves. The blood pressure was obtained before and several times during a three to eight-hour period after administration of the test drug. Priscol was given orally, intramuscularly and also intravenously. Etamon, SC 1950, C 7337 or C 5968 were given intravenously and also intramuscularly. Dibenamine was given intravenously only. Three or more tests were performed for each route of administration. The effect of priscol was variable, pressor responses occurring occasionally, and a significant to normal reduction of blood pressure in one-half of the experiments also occurring. Dibenamine caused reduction of the pressure to normal and this lasted fifty hours in one dog. C 7337 and C 5968 reduced the blood pressure to normal. Etamon reduced the pressure to normal in one-half of the trials while GD 1950 had the same effect in all animals but one. In unanesthetized normal animals the aforementioned drugs caused changes in blood pressure varying from an increase to moderate decrease.

EFFECT OF HIGH SPINAL ANESTHESIA ON THE CARDIAC OUTPUT OF NORMAL AND HYPERTENSIVE PATIENTS. *Lawrence G. May, M.D., Alene Bennett, M.D., A. L. Lane, M.D., E. D. Futch, M.D., Mary Lynn-Schoomer, M.D. (by invitation) and Raymond Gregory,*

M.D. From The University of Texas Medical Branch, Galveston, Tex.

In attempting to arrive at some understanding of the pathogenesis of essential hypertension, high spinal anesthesia has been used as a method of producing a decrease in blood pressure in patients with essential hypertension. The degree to which elevated blood pressure may be lowered uniformly with high spinal anesthesia has suggested the importance of an increased vasomotor tone in maintenance of the arteriolar constriction. Opponents to this idea have argued that the drop in blood pressure is due to diminished venous return to the heart which produces a decrease in the cardiac output sufficient to explain the fall in blood pressure.

Other studies of the relationship between venous and arterial pressure under high spinal anesthesia have shown no correlation in the time relationships between the falls of venous and arterial pressures. In most instances the arterial pressure falls before the venous pressure. From this somewhat indirect evidence it has been believed that the fall in arterial pressure cannot be explained on the basis of diminished cardiac output. It was decided, however, that cardiac output studies must be done in order to make final conclusions and such studies were made employing the direct Fick method.

One hundred seventeen cardiac output determinations have been done on fifteen normotensive and seven hypertensive individuals: (1) Unsedated normotensives with spinal anesthesia, (2) sedated normotensives with spinal, (3) unsedated normotensives without spinal, (4) sedated normotensives without spinal, (5) sedated hypertensives with spinal, (6) unsedated hypertensives with spinal, (7) sedated hypertensives without spinal, (8) unsedated hypertensives without spinal.

In the normotensive patients the control cardiac indices before spinal anesthesia are so high and so variable that it is impossible in most instances to get a base line within the normal range. In this group spinal anesthesia causes a fall in the cardiac index but the fall is always within the normal range. In the sedated normotensives the control cardiac indices are essentially within the normal range; spinal anesthesia causes some slight fall but the fall is essentially within the normal range. We were somewhat surprised to find the cardiac indices

of unsedated hypertensives to be uniformly within the normal range and often to be below the commonly accepted normal range, and to find that the sedated hypertensive individual often has a slightly higher cardiac index than the unsedated.

In the sedated hypertensives with high spinal anesthesia there was little if any fall in the cardiac index in spite of a uniformly obtained fall in both systolic and diastolic blood pressure. The falls in cardiac index that did occur in the hypertensive group were usually still within normal range and were no greater than the falls which occurred in the control groups of hypertensives which were sedated; a spinal tap was done but no spinal anesthesia was induced. Hypertensive patients under spinal anesthesia uniformly had higher cardiac indices than a group without spinal anesthesia.

In normotensives high spinal anesthesia associated with the fall in blood pressure may not be associated with a significant fall in cardiac index if the control values are within normal limits before the spinal anesthesia is induced unless the blood pressure falls below critical levels of 80 to 90 mm. Hg systolic. In the hypertensive group, use of a high spinal anesthesia which is associated with a great fall in the blood pressure, we usually did not find a significant fall in the cardiac index. The variations which occurred were usually within the normal range.

In both normotensive and hypertensive individuals significant falls in blood pressure may occur without any significant fall in cardiac index.

Read by Title

OBSERVATIONS ON REGULATION OF THE CEREBRAL CIRCULATION. *Peritz Scheinberg, M.D. (by invitation) and Eugene A. Stead, Jr., M.D.* From Duke University School of Medicine, Durham, N. C.

The purpose of this study was to determine the ability of the cerebral blood vessels to dilate and constrict in response to various physiologic and pathologic situations. The cerebral blood flow was measured by the nitrous oxide method of Kety and Schmidt. The cerebral O₂ and glucose consumptions were calculated by multiplying the respective arterio-internal jugular differences by the cerebral blood flow. The peripheral resistance was calculated in absolute

units by dividing the mean pressure by the blood flow.

Observations have been made in normal subjects in the recumbent position and after motionless standing. Patients with hypertension who have recovered from removal of the sympathetic chain from I_1 through the stellate ganglia were studied in the recumbent and standing positions. The effects of stellate block in patients with cerebral vascular disease have been observed.

IMPROVEMENT OF THE ARTIFICIAL KIDNEY: AN EXPERIMENTAL STUDY OF ITS APPLICATION TO DOGS DEPRIVED OF RENAL EXCRETORY FUNCTION. *John Vanatta, M.D. (by invitation), E. E. Muirhead, M.D. and Arthur Grollman, M.D.* From The Departments of Physiology and Pharmacology, Pathology and Experimental Medicine, Southwestern Medical College, Dallas, Tex.

The artificial kidney has been applied 120 times to eighty-five dogs, seventy-five of which were deprived of renal excretory function by bilateral nephrectomy or other procedures. Study of the technic as described by Kolff and other workers revealed the following fundamental defects: (1) the composition of the bath not only failed adequately to maintain the normalcy of the chemical composition of the blood but in addition produced hemolysis; (2) the membrane reacted with blood to cause hemolysis; (3) the pump on the original apparatus of Kolff caused hemolysis; (4) the dosage of heparin had to be adjusted, and antiheparin substances were needed to prevent hemorrhage from the wound and (5) variations in the blood content of the apparatus resulted in depletion or overload of the vascular system.

Following alteration of the bath and chemical treatment of the membrane as well as attention to other details, nephrectomized dogs were maintained to the twentieth day and dogs otherwise deprived of renal excretory function for a period of a month, at which time they were sacrificed for pathologic study.

PATHOLOGIC CHANGES IN BILATERALLY NEPHRECTOMIZED DOGS WITH HYPERTENSION. *E. E. Muirhead, M.D., John Vanatta, M.D. (by invitation) and Arthur Grollman,*

M.D. From The Departments of Physiology and Pharmacology, Pathology and Experimental Medicine, Southwestern Medical College, Dallas, Tex.

Bilaterally nephrectomized dogs sustained with the artificial kidney develop a characteristic pattern of lesions. Early changes occur by the fifth day, definite lesions by the eighth day and advanced lesions thereafter. The main changes are found in smooth muscle tissue throughout the body. Arteries, veins and arterioles display the following: loss of longitudinal striations, hyaline swelling, pyknosis, disappearance of nuclei and confluence of hyalinized fibers with a smudgy appearance. Infarcts are noted in the myocardium, gastrointestinal mucosa and intestinal muscularis. Smooth muscle changes are also noted in the muscular coats of the esophagus, stomach, small and large intestine, splenic trabeculae and urinary bladder. The bronchial tree and pulmonary vessels do not reveal these changes. Hyaline emboli are encountered in the heart, gastrointestinal mucosa and lungs. Bilateral ligation of the ureters culminate in similar findings. Implantation of the ureter into the small bowel with contralateral nephrectomy and sustenance up to thirty days has not caused these changes.

The vascular changes are those of malignant hypertension. Widespread smooth muscle tissue changes seem evident in this condition.

HEMATOLOGIC ABNORMALITIES RESULTING FROM METASTASES OF PROSTATIC CARCINOMA TO BONE MARROW. *U. Jonsson, M.D. (by invitation) and R. W. Rundles, M.D.* From The Duke University School of Medicine, Durham, N. C.

The growth of tumor metastases within the bone marrow may produce fever, skeletal pain, roentgenologically demonstrable bone lesions and/or anemia before there is local evidence of neoplastic growth. Hematologic studies may establish the diagnosis and aid in evaluating the response to therapy.

Bone marrow aspirations in twenty-eight patients with prostatic cancer, nineteen of whom had x-ray or other evidence of tumor metastases, revealed tumor implants in sixteen subjects. Among those with metastases the prostate gland was considered by palpation to be benign in four cases. Five had questionable neoplastic

nodules. Osteoblastic skeletal lesions were present in fourteen patients. The acid phosphatase was above 3 King-Armstrong units in sixteen and the alkaline phosphatase above 10 King-Armstrong units in seventeen patients. A useful physical sign—pronounced tenderness over the sternum—was present in thirteen of those with marrow metastases.

The hemoglobin was less than 12 Gm./100 cc. in sixteen patients. Severe anemia of the leuko-erythroblastic type, with immature granulocytes and nucleated red blood cells in the circulating blood, was present in eight patients with gross infiltration of the bone marrow with tumor tissue. Tumor cells were found in the bone marrow of two patients who had no x-ray abnormalities and normal phosphatase and peripheral blood values.

Six of the patients with leuko-erythroblastic anemia associated with tumor metastases in the bone marrow were followed for four to eleven months after orchidectomy and estrogen therapy. The peripheral blood values improved or became normal in five months. Tumor cells in the bone marrow decreased in number, their cytoplasm became denser and the nuclei pyknotic. Progressive bony sclerosis of a degree making needle biopsy impossible was observed without development of anemia. The degree of tumor infiltration increased in one patient and the blood values continued to fall.

EFFECT OF ADRENOXYL ON BLOOD LOSS FROM SURGICAL WOUNDS. *J. J. Zavertnik, M.D., R. F. Hagerty, M.D. (by invitation) and K. S. Grimson, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Adrenoxyl, a mono-semicarbazone of adrenochrome, reportedly decreases bleeding time of rabbits and man. Our studies confirm the effect on bleeding time. In dogs an intramuscular injection of 10 gamma of adrenoxyl produced a marked decrease, the effect becoming maximal at thirty to sixty minutes. A study of the ability of the drug to decrease blood loss from surgical wounds also has been made.

Consecutive parallel and apparently similar incisions were made in the liver of anesthetized dogs estimating bleeding by weight of the blood collected. One hour after administration of 10 gamma of adrenoxyl bleeding decreased markedly with one exception in which it was

apparent that severance of a large vessel increased bleeding and masked the effect of adrenoxyl.

The amount of blood loss from wounds produced by the resection of similar portions of a rabbit's ear was also estimated and was found to be decreased moderately one hour after administration of 10 gamma of adrenoxyl. This effect was measured by producing the same type of wounds on opposite ears of the same rabbit five days apart. Three different wounds produced on one ear before administration of the drug bled an average of .31 Gm., .72 Gm., .80 Gm. of hemoglobin, respectively, increasing amounts representing the larger or more proximal incisions. Five days later three similar wounds were made using the opposite ear and administering adrenoxyl. Decrease in bleeding after administration of adrenoxyl was 44.7 per cent, 3.7 per cent and 13.3 per cent, respectively. The effect of adrenoxyl appeared more marked in wounds in which bleeding was predominantly from small vessels. An attempt was also made to study the amount of bleeding from donor sites of skin grafts and from multiple skin incisions, but wide variations of bleeding occurring in control studies prevented studying the effects of adrenoxyl on blood loss from these wounds.

Adrenoxyl appears to decrease the bleeding time and amount of blood loss from wounds in which the bleeding is a slow, steady ooze. Because of encouraging results obtained so far, clinical trials have been started and will be discussed at a future date.

CIRCULATING RED CELL MASS IN POLYCYTHEMIA VERA AS DETERMINED BY RED BLOOD CELLS TAGGED WITH THE RADIOACTIVE ISOTOPE OF IRON. *George R. Meneely, M.D., E. B. Wells, M.D. (by invitation) and Paul F. Hahn, M.D.* From The Department of Medicine, Vanderbilt University School of Medicine and the Cancer Research Laboratories, Meharry Medical College, Nashville, Tenn.

Previous reports by ourselves and others have shown a pronounced difference between antecubital venous hematocrit and the average body hematocrit when the plasma volume is measured by the method of Gibson and Evans and the red cell mass by the method of Hahn, Ross, Balfour, Bale and Whipple as modified by Meneely, Wells and Hahn. Although under

normal conditions it is true that the venous hematocrit reflects proportionately the circulating red cell mass, in conditions such as inanition, shock, cardiac failure, polycythemia vera, etc., such a relationship probably does not occur and the venous hematocrit does not afford a

TABLE I

Patient	Weight	Red Blood Cells	Hemato-crit (vol. %)	Red Cell Mass (ml.)			
				Normal	Estimated	Deter-mined	Excess
J. W.	85	10.8	67	2300	3400	6200	2800
C. Y.	70	8.0	61	1890	2560	3960	1400

true picture of the existing state of affairs in the circulation. We present data in two patients to show that by direct determination the total circulating red cell mass is considerably greater than that which would be estimated on the basis of body weight and venous hematocrit.

From this data it is seen that the observed red cell mass is much greater than would be expected on the basis of antecubital venous hematocrit and body weight. We believe that many failures in therapy of polycythemia by phlebotomy are ascribable to a lack of comprehension of the extent of the plethora and polycythemia actually present which leads to gross undertreatment. Properly employed, phlebotomy is a physiologic and adequate therapy. Such is not the case with phenylhydrazine which incites reticulocytosis, is toxic and releases detritus in the vascular bed of patients already threatened with thrombotic accidents. We have stated before and reiterate our opposition to radioactive phosphorus in this condition, which is almost invariably benign, because we believe phosphorus as a relatively long-lived isotope is not suitable for therapy and because of the danger of precipitating a fulminating leukemia.

DEMONSTRATION OF ADRENOCORTICO-TROPHIC HORMONE IN THE URINE OF TWO FEMALE PATIENTS WITH CUSHING'S SYNDROME. *Albert Segaloff, M.D. and William Parson, M.D.* From The Department of Medicine, Tulane University School of Medicine, and the Alton Ochsner Medical Foundation, New Orleans, La.

Two female patients with classical Cushing's syndrome have been studied. They both fitted

the usual criteria with thin skin, striae, atrophic muscles, plethoric facies, "buffalo obesity," hypertension, etc. In addition they had markedly elevated urinary excretions of cortin (biological assay) and one of them had an (intermittently) elevated urinary excretion of 17-ketosteroids. This latter patient died from an overwhelming infection of *Cryptococcus hominis*. The post-mortem examination revealed bilateral adrenal cortical hyperplasia and Crooke cell changes in the pituitary. The other patient is still under observation and it is believed that she, too, has bilateral adrenal cortical hyperplasia.

The assays for adrenocortrophic hormone in the urine were done by the Sayers and Sayers technic based on depletion of adrenal ascorbic acid in hypophysectomized rats. The most satisfactory urinary concentrates were achieved by a modified alcohol precipitation dialysis method. In the best studies the animals each received intravenously the concentrate from twelve hours of urine.

Urinary concentrates from normals and from patients with various diseases were assayed in parallel with the concentrates from patients with Cushing's syndrome. The controls were consistently negative. (The controls included patients with proven adrenal cortical hyperplasia with virilism, "the adrenogenital syndrome.")

The two patients reported here represent the only instances we have found of unequivocal evidence of urinary excretion of adrenocorticotrophic hormone.

SERUM CHOLESTEROL ESTERASE IN NORMAL DIABETIC AND ARTERIOSCLEROTIC PATIENTS. *E. D. Futch, M.D. (by invitation) and Raymond Gregory, M.D.* From The University of Texas Medical Branch, Galveston, Tex.

In early atherosclerotic changes cholesterol esters exceed free cholesterol. In old atherosclerotic deposits the percentage of free cholesterol increases. The degree to which cholesterol esterase activity might be a factor in the intimal deposition of cholesterol or its esters is the basis for the studies that are being reported here.

In vitro studies of the extent and rapidity of the conversion of free cholesterol to cholesterol esters resulting from the incubation of serum in ten normal, ten diabetic and ten patients with severe arteriosclerotic disease have been made according to the method of Sperry. Serum from

the aforementioned types of patients was analyzed for cholesterol fractions at zero hours and after twenty-four, forty-eight and seventy-two hours incubation at 37°c. under sterile conditions. The rate and degree to which free cholesterol was converted to cholesterol esters varied within wide limits. We were, however, unable to detect any significant change in these values in the normal diabetic and arteriosclerotic groups. From these data it is concluded that abnormalities of serum cholesterol esterase do not play a significant role in the pathogenesis of atherosclerosis.

EFFECTS OF A QUATERNARY AMINE ON FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM. *F. H. Longino, M.D. (by invitation), J. R. Chittum, M.D. (by invitation) and K. S. Grimson, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Effects of 2,6 dimethyl diethyl piperidinium bromide on functions of the autonomic nervous system have been determined. In anesthetized dogs the drug lowered arterial blood pressure and blocked changes of pressure normally occurring with the carotid sinus reflex, stimulation of central and peripheral ends of divided vagi and anoxia. It also equalized changes of peripheral resistance of normal and sympathectomized extremities during these stimuli. Pressor responses to intravenous epinephrine were apparently increased. Terminal increase of blood pressure normally associated with acute rise of intracranial pressure was not prevented. Effects of the drug were counteracted by prostigmine.

In normal unanesthetized dogs moderate increases of blood pressure and tachycardia occurred after administration of the drug. In dogs with chronic neurogenic hypertension the drug caused a reduction of blood pressure and a slowing of the pulse. Barium studies of the gastrointestinal tracts of normal dogs showed that small doses stimulated gastric and intestinal activity but that larger doses effected cessation of peristalsis of the stomach and delayed transit through the small intestine.

In patients the drug abolished activity of the stomach and small intestine as shown by balloon intubation studies. Barium studies demonstrated delay of gastric emptying and of transit through the small intestine. Effects on the gastrointestinal tract were partially counter-

acted by urecholine. In normotensive patients a transient fall of blood pressure occurred. This was more marked and prolonged in hypertensive patients. Reduction or reversal of normal pressor responses to breath holding or application of cold was effected as was loss of the temperature gradient of each extremity, paralysis of accommodation, dilatation of the pupils and ptosis of the upper eyelids.

Actions of this new drug were apparently much like those of the tetraethylammonium ion, and since these actions were reversed by prostigmine it seems likely that cholinergic synaptic transmission through autonomic ganglia is blocked.

RESPONSE OF LINGUAL MANIFESTATION OF PERNICIOUS ANEMIA TO PTEROYLGUTAMIC ACID AND VITAMIN B₁₂. *James F. Schieve, M.D. (by invitation) and R. W. Rundles, M.D.* From The Duke University School of Medicine, Durham, N. C.

While the therapeutic effectiveness of synthetic pteroylglutamic acid is satisfactory in the majority of patients with pernicious anemia, macrocytic anemia often is not completely corrected and neurologic relapses may occur on maintenance doses. Little attention has been paid to the third major clinical manifestation of the disease, that of atrophy and inflammation of the lingual mucosa.

Seven patients with pernicious anemia in relapse having lingual mucosal atrophy were given 30 to 100 mg. of pteroylglutamic acid daily by mouth. In two the filiform papillae regenerated to normal height in seven to ten days, a response equal to that regularly obtained by fully potent liver therapy. In five patients the lingual response from the beginning of therapy was poor. Their tongues tended to remain red and the papillae stubby. During the third month of pteroylglutamic acid therapy two of these patients had definite lingual relapses, developing sore, red and completely smooth tongues. They were given intramuscular injections of 0.010 and 0.025 mg. of vitamin B₁₂. Regeneration of filiform papillae and restoration of the normal lingual color followed in six to seven days.

Five patients with untreated pernicious anemia in relapse who also had lingual manifestations of the disease were given 0.001 mg. daily or a single dose of 0.010 mg. of vitamin

B₁₂. Regeneration of the papillae and restoration of a normal lingual color followed in six to ten days.

Pteroylglutamic acid may fail to induce and maintain remissions of lingual manifestations of pernicious anemia as well as the anemic and neurologic manifestations. Vitamin B₁₂ produced rapid regeneration of the lingual mucosa in patients with pernicious anemia who relapsed under pteroylglutamic therapy and in those who had no previous treatment.

VIRUS ISOLATION AND SEROLOGIC STUDIES IN PATIENTS WITH CLINICAL MUMPS. *William F. Friedewald, M.D. (introduced by Paul B. Beeson, M.D.)* From The Department of Bacteriology and Immunology, Emory University School of Medicine, Atlanta, Ga.

Materials from patients with various manifestations of mumps were tested for virus by the amniotic method of inoculation into embryonated eggs. Mouth washings from seventeen patients obtained within three days after the onset of parotitis yielded virus in ten of the specimens (59 per cent). Virus was also recovered from the testicular tissue of one patient with orchitis. Virus was not detected in (1) the saliva from three patients which was taken seven days after the onset of parotitis, (2) the spinal fluid of seven patients with meningoencephalitis, (3) hydrocele fluid of two patients with orchitis, (4) the blood of three patients taken during the first or second day of illness and (5) a placental extract from a patient with parotitis.

Agglutination inhibition and complement fixation tests on sera from fifteen patients with parotitis showed comparable rises in the titer of the antibodies. The complement fixation test, however, appeared to be more reliable and gave more reproducible results. No major differences in the antigenic structure of a stock strain of mumps virus and two viruses isolated in the present work were apparent in the tests with human sera or with antisera prepared in chickens against these viruses.

STUDIES IN THE FRACTIONATION OF LIVER. COMPOSITION OF REGENERATING LIVER AFTER PARTIAL HEPATECTOMY IN RATS. *Alfred Chanutin, M.D. and (by invitation) Erland C. Gjessing, M.D.* From The De-

partment of Biochemistry, University of Virginia School of Medicine, Charlottesville, Va.

The rate of regeneration of the liver following partial hepatectomy is greatest during the second, third and fourth days as judged by the wet and dry weights and nitrogen contents. The percentage concentration of the total solids decreases during the first three postoperative days. The respective control values are not reached by the fourteenth day.

A procedure is described for fractionating liver into three fractions: (a) a saline insoluble residue; (b) a precipitate obtained from the dialyzed saline extract at pH 5.8 and (c) ethanol-precipitated proteins.

The total solid and nitrogen contents of each of the three fractions are decreased to the same extent on the first postoperative day and increase at approximately the same rate on subsequent days. During the first and second postoperative days excessive amounts of lipide are present in Fractions a and b. Subsequently the lipides are incorporated in these two fractions in about the same proportions noted for nitrogen. Fraction c contains traces of lipide carbon and is devoid of cholesterol. The total lipide carbon and cholesterol concentrations of the liver mitochondria are not affected by partial hepatectomy. The respective relative proportions of the total solids, nitrogen and total lipide in the three liver fractions are relatively constant during liver regeneration.

The conclusion to be drawn from this investigation is that the major components of three distinctly different liver fractions are regenerated at approximately the same rate following partial hepatectomy.

LACK OF PITUITARY GONADOTROPHINS ASSOCIATED WITH ADRENAL ANDROGEN DEFICIENCY. *Laurence H. Kyle, M.D. (Introduced by Harold Jeghers, M.D.)* From The Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

A negro female, nineteen years of age, showed primary amenorrhea, hypogenitalism, lack of mammary development, absence of axillary and pubic hair and eunuchoid skeletal proportions, the ratio of trunk to lower extremities being .92. Additional findings were a number of

congenital defects including an arteriovenous fistula of the left forearm, nystagmus, partial optic atrophy and moderate cardiac enlargement. There was no family history of any similar disorder. Laboratory examination revealed pituitary gonadotrophins negative for 6 mouse units and urinary 17-ketosteroids averaging 1.5 mg. per twenty-four hours. Glucose tolerance test and insulin tolerance tests were normal. The basal metabolic rate was within normal limits. On the basis of these findings it was decided that the patient fitted none of the usual groups associated with hypogenitalism. Considered probable was a diagnosis of primary gonadotrophin deficiency together with deficiency of whatever trophic hormone stimulates adrenal androgen production. Search of the literature revealed a report of one similar case.

The pattern of the disease appeared suitable for testing the postulation of Albright and Reifenstein in regard to stimulation of adrenal androgen production by the luteinizing hormone. Consequently the patient was studied from several viewpoints during administration of large amounts of luteinizing hormone in the form of chorionic gonadotrophin (A.P.L.).

During her course of therapy the patient showed quite marked breast development together with cornification of previously atrophic vaginal epithelium. Such evidence of estrin production is not in accordance with our present concepts of action of chorionic gonadotrophin. Possible explanations of these changes will be discussed at a later date.

VITAMIN B₁₂, PTEROYLGUTAMIC ACID AND LIVER EXTRACT IN THE TREATMENT OF MACROCYTIC ANEMIA. *Grace A. Goldsmith, M.D.* From The Department of Medicine, Tulane University School of Medicine, New Orleans, La.

An increase in reticulocytes, erythrocytes and hemoglobin followed administration of vitamin B₁₂ to six patients and pteroylglutamic acid to twenty-four patients with macrocytic anemia in relapse. Findings will be compared with the response to liver extract. A normal or slightly subnormal blood picture was maintained in twelve patients for more than six months with 5 mg. of pteroylglutamic acid daily. Doses of 2.5 mg. per day were equally effective in two patients with sprue and two with nutritional macrocytic anemia, but the blood count fell

in two patients with pernicious anemia. Liver extract, 15 to 30 units weekly, maintained the erythrocyte count and hemoglobin at higher levels than did 5 to 30 mg. of pteroylglutamic acid daily in four or five patients. Substitution of vitamin B₁₂ for pteroylglutamic acid in one patient was followed by improvement in the blood picture.

Of nine patients with pernicious anemia treated with pteroylglutamic acid two developed a neurologic relapse during therapy while existing neurologic changes in two others were unaffected. Neurologic abnormalities were reversed by vitamin B₁₂ in one patient who received this therapy.

ROLE OF THE KIDNEY IN THE STORAGE OF IRON. *John K. Hampton, Jr., M.D. (Introduced by H. S. Mayerson, M.D.)* From The Department of Physiology, Tulane University School of Medicine, New Orleans, La.

Studies by Granick and others have shown that iron is stored chiefly in the liver, spleen and bone marrow as the protein-iron compound, ferritin. Evidence is also available to indicate the presence of ferritin in crystallizable amounts in the kidneys of the cat and the dog. Its presence in the horse kidney has been demonstrated in minute amounts.

The present experiments extend these findings to the mouse and rabbit kidney. Attempts to crystallize ferritin by the CdSO₄ method from animals using the usual laboratory regimen were unsuccessful. However, when hemoglobin or iron compounds were injected intraperitoneally, large amounts of ferritin appeared in the mouse kidneys and in some of the rabbit kidneys. The amount of ferritin present appeared to be correlated with the dose of iron administered. The significance of these findings is being investigated.

EFFECT OF METHADON ON ERYTHROCYTE PERMEABILITY IN VITRO AND ITS POSSIBLE CONNECTION WITH CHOLINESTERASE ACTIVITY. *Margaret E. Greig, M.D. and (by invitation) William C. Holland, M.D.* From The Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn.

In some metabolic studies *in vitro* in this laboratory it was found that methadon (amidone) inhibited glycolysis of glucose by the rat brain. It was also found to inhibit cholinesterase activity.

In some experiments *in vivo* on dogs it was found that intravenous administration of methadon was frequently but not always followed by a hemoglobinuria. This was accompanied by an increase in erythrocyte fragility. In some experiments *in vitro* methadon also produced an increase in fragility of erythrocytes. This increase in fragility of erythrocytes might be due to the inhibition of glycolysis by methadon, as Wilbrandt reported changes in permeability of erythrocytes exposed to sodium fluoride or to sodium iodacetate which are known to be glycolytic inhibitors. However, sodium fluoride and sodium iodoacetate also inhibit cholinesterase activity in the concentrations used by this author and it would seem possible that inhibition of this enzyme might be involved in the changes observed. To test this possibility the effects of prostigmine and physostigmine, which are specific inhibitors of cholinesterase, were investigated and it was found that these drugs also produced changes in permeability of erythrocytes. The results of these experiments with physostigmine and prostigmine as well as those with methadon seem to indicate that inhibition of cholinesterase activity, rather than or in addition to inhibition of glycolytic enzymes, may be involved in changes in permeability of the erythrocyte membrane. Experiments on the changes in cation concentration of erythrocytes exposed to methadon and other inhibitors of cholinesterase are in progress.

DETERMINATION OF CIRCULATING RED BLOOD CELL VOLUME WITH RADIOACTIVE PHOSPHORUS. *R. T. Nieset, M.D., Blanche Porter, M.D., W. S. Trautman, Jr., M.D., Ralph M. Bell, M.D. (by invitation) and William Parson, M.D., Champ Lyons, M.D. and H. S. Mayerson, M.D.* From The Laboratory of Biophysics, Departments of Medicine, Surgery and Physiology, School of Medicine, Tulane University and the Alton Ochsner Medical Foundation, New Orleans, La.

A simple dilution method for direct measurement of total circulating red blood cell volume using radioactive phosphorus (P-32) has been

developed. The red cells from the subject of study are utilized for labelling. Whole blood samples are used for counting so that no chemical or physical separation of the trace element is required. The validity of the method has been proved by independent studies in patients of the rate of absorption and of loss of radioactive phosphorus by red cells *in vivo* and *in vitro* and of the loss of phosphorus from the plasma *in vivo*. These experiments show that the P-32 is taken up rapidly by red cells and released slowly. The ease of counting and opportunity for repetitive measurement have proved to be advantageous in the clinical exploitation of the method.

IN VITRO PROPERTIES OF CORYNEBACTERIUM DIPHTHERIAE STRAINS ISOLATED FROM DIPHTHERIA PATIENTS IN LOUISIANA. *M. F. Shaffer, M.D.* From The Department of Bacteriology, Tulane University School of Medicine, New Orleans, La.

Several European workers have observed a fair degree of correlation between the clinical severity of diphtheria cases in local outbreaks and the varieties of *C. diphtheriae* (gravis, intermedius and mitis) responsible. American investigators have hitherto been unable to demonstrate a similar relationship for the organisms isolated from diphtheria patients in this country. Gravis strains have been obtained from healthy carriers in certain of the Southern states but epidemics have not developed in the communities where these bacteria were found. Because of the need for further data bearing on the latter point and the availability of clinical material, during the early winter of 1945 to 1946 a series of diphtheria patients at the Charity Hospital, New Orleans, La., were studied in collaboration with Dr. Kay Kohara.

The seriousness of the disease varied from mild (eight cases), moderately severe (eight cases) and very severe (six cases) to fatal (two cases). No gravis strain was recovered from any of these patients. From eighteen patients, chiefly those with diphtheria of moderate or considerable severity and including one of the fatal cases, typical mitis strains were obtained while from the remaining six patients, with mild, severe or fatal disease, strains differing from mitis but not identical with the intermedius variety were isolated. Of the twenty-four strains of toxigenic diphtheria bacilli three proved capable of fermenting sucrose; use of this fer-

mentation reaction as a test for differentiating *C. diphtheriae* from non-pathogenic diphtheroid bacilli is thus undependable.

FIELD SPREAD PHENOMENA RELATED TO ELECTRICAL STIMULATION OF THE LATERAL OLFACTORY TRACT IN THE CAT.
James W. Ward, M.D. From The Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tenn.

Using a unipolar recording method a positive wave ($\frac{1}{50}$ sec. long) was picked up from all parts of the brain substance and the overlying bone and muscles. This activity resulted from electrical stimulation of the olfactory brain from the bulb back through the lateral olfactory tract to the region of the amygdaloid nuclei as far back as the optic chiasma. Direct nerve conduction was demonstrated from the bulb back to this anterior region of the piriform lobe. The positive wave appears to be a field spread current from the posterior region from which it can be elicited because: (1) it was not recorded with closely spaced bipolar leads unless they were in the "center" of origin, (2) no difference in latency of the response was noted with rapid sweeps on the C.R.O. no matter in what part of the head the unipolar pickup lead was located, (3) the response was not lost anywhere in or on the surface of the brain after a mid-sagittal section of the brain from the front backward to the level of the pons, nor was it affected by an additional hemisection of the brain behind the optic chiasma on the side which was stimulated. Section of the brain in the region of the lateral olfactory tract behind the stimulation electrode abolished the response. This response was negative when the recording lead was on the under surface of the brain below the region of distribution of the lateral olfactory tract (results comparable to those of Fox, McKinley and Magoun, 1944). The response is discussed in relation to a possible relationship with the E.E.G. under certain conditions.

FACTORS INFLUENCING CONTRACTILE FORCE OF THE HEART. *R. P. Walton, M.D., H. H. Brill, M.D., and M. DeV. Cotten, M.D.* (Introduced by Harold Green, M.D.) From The Department of Pharmacology, Medical College of South Carolina, Charleston, S. C.

The contractile force of a section of the right ventricle has been determined directly by introducing varying spring tensions into the classic Cushny heart lever system typically attached in the open-chest dog preparation. Changes in heart size are compensated for by mechanical adjustment or by a preliminary calibration procedure. Various maneuvers were conducted under relatively standardized conditions. Application of measured degrees of stretch to muscle section progressively increased the contractile force (isometric systolic tension) in extreme instances up to 600 per cent of that in the control period. Coronary ligation markedly decreased contractile force. Stenosis of the inferior vena cava, venous hemorrhage and arterial hemorrhage did not greatly affect contractile force until after substantial decrease in systemic arterial pressure. Saline infusions at the rate of 10 cc./Kg. over the period of about two minutes consistently raised venous pressures about 15 mm. with only insignificant effects on contractile force. (The same infusion rate in the intact animal markedly raises venous pressure.) Infusions at the rate of 20 to 40 cc./Kg. during the same period raised venous pressures 30 to 65 mm. with only limited or moderate effects on contractile force. Cardiotonic drugs (sympathomimetic group, veratrine and cardiac glycosides) moderately elevate venous pressure when they produce increases in contractile force. Metrazol, presumably without direct cardiac effects, increased contractile force 20 to 30 per cent under hypotensive conditions when there were substantial increases in the arterial pressure following the injection.

In summary, under these experimental conditions, contractile force is greatly increased by mechanical stretching but is only nominally affected by the degree of pressure changes occurring through ordinary variations in venous flow. When there is a serious degree of hypotension, an increase in arterial pressure increases contractile force possibly through an increase in coronary flow.

AMINOPTERIN THERAPY IN ACUTE LEUKEMIA. *Roy R. Kracke, M.D. and (by invitation) William H. Rice, Jr., M.D.* From The Department of Medicine, Medical College of Alabama, Birmingham, Ala.

Farber and associates recently reported that temporary remissions in acute leukemia in

children could be produced by certain folic acid antagonists. Since their original report, aminopterin (4-aminopteroylglutamic acid) has been used in the treatment of acute leukemia in twenty-two children and five adults in our clinic. Of the twenty-seven patients treated twelve are living and fifteen are dead. Aminopterin produced temporary clinical remissions in five of the living patients and significant temporary hematologic changes in others in the series. Those who experienced temporary remissions had no clinical symptoms and their blood and bone marrow appeared normal. The response was not consistent in all cases.

Toxic manifestations of aminopterin are: anorexia, ulcerations of the buccal mucosa,

glossitis, stomatitis, diarrhea, ulceration of the gastrointestinal mucosa and aplasia of the bone marrow. Toxic manifestations usually clear up four to five days after discontinuance of therapy. Aminopterin can be started again in small doses and increased to tolerance or until the desired effect is obtained.

The patients in our study can be classified into three groups: (1) Those in whom aminopterin had no appreciable effect, (2) those whose leukemia was apparently controlled temporarily but blood and bone marrow remained abnormal and (3) those experiencing temporary clinical remissions with absence of symptoms and a normal-appearing blood and bone marrow pattern.

Case Reports

Thyrotoxicosis Simulating Hyperparathyroidism*

MALCOLM M. STANLEY, M.D. and JOSEPH FAZEKAS, M.D.

Boston, Massachusetts

Washington, D.C.

WHEN a patient complains of typical symptoms and exhibits characteristic signs, the diagnosis of thyrotoxicosis is easily made. In some instances, however, many of these symptoms are lacking and the diagnosis is difficult. In such cases it is often necessary to obtain assistance from special laboratory procedures. Recently it has been found that determination of the accumulation of radioactive iodide by the thyroid gland is useful in diagnosis of thyrotoxicosis.¹³

The present report concerns a patient with thyrotoxicosis whose disease was obscured by the absence of many characteristic features and by the presence of azotemia, hypercalcemia and a normal heart rate. The greatly increased uptake of radio-iodide pointed to the diagnosis which, however, was established definitely only after repeated studies before and after treatment with antithyroid drugs.

CASE REPORT

L. D., a forty-four year old male clerk, entered the Pratt Diagnostic Hospital on June 9, 1947, because of vomiting, weakness, weight loss and nervousness. He was well until four months before when his muscles became stiff, lame and weak. He "felt shaky inside." Several days later his ankles became swollen. The stiffness of the muscles was pronounced for approximately two weeks and never completely left him. There was some intolerance to heat, in that he became uncomfortable with the usual bedclothing. He believed that his urine was darker than normal. Nocturia which had been present for years continued unchanged until admission. The bowel habits were normal, there was no diarrhea

and the stools were constantly brown. Two weeks after the onset of his illness the first attack of vomiting occurred. There was no abdominal pain or distention, "just a feeling of uneasiness over my stomach," and for several days he was unable to retain solids or liquids. Before the first admission there were five such episodes of vomiting, each lasting for three to seven days. He was, therefore, unable to eat normally and in four months lost approximately 50 pounds. He became progressively weaker, nervous and shaky and noted palpitation, dyspnea and exhaustion on slight exertion.

He had been hospitalized elsewhere on three occasions because of these complaints. Laboratory studies had included urinary specific gravities of 1.026 (February 25, 1947), 1.025 (March 14, 1947) and 1.015 (May 6, 1947). The last two urinalyses also had revealed 1+ albumin and a few granular casts. Examinations of the gastrointestinal tract, gallbladder and liver had shown no abnormalities.

Upon physical examination it was seen that the patient was quite ill, debilitated and cachectic but well oriented. The skin was pale, tanned, warm and dry; the palms were hot and dry. The eyeballs appeared to be sunken. The thyroid was smooth, firm and slightly enlarged but there was no bruit or thrill. The heart was normal in size, the beat was forceful and a grade II systolic murmur was heard over the precordium. The heart rate was 88 per minute. There was some muscle tenderness over the left arm and forearm and a rather coarse tremor of the fingers was present. The remainder of the physical examination revealed no abnormalities.

Laboratory data revealed that the urine was free of sugar and tests for albumin were 1+ to 2+. A few white cells, red cells and occasional hyaline and granular casts were noted. The

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specific gravity on three examinations was 1.009, 1.010 and 1.012. After withholding fluids for sixteen hours the specific gravity was 1.013 on one occasion. A value of 1.013 was obtained after 1 cc. pitressin. The urinary phenolsulfon-phthalein excretion was 15 per cent in fifteen

Gm. of globulin. The serum alkaline phosphatase was 3.4 Bodansky units per 100 cc. The blood carbon dioxide capacity was 69 volumes per cent. The blood non-protein nitrogen was 49 mg. per 100 cc. on two occasions.

X-rays showed the bones of the hands, skull,

TABLE I
SUMMARY OF PERTINENT DATA BEFORE AND DURING THE COURSE OF TREATMENT

Date	Calcium Intake (Gm./day)	Urinary Calcium (Gm./day)	Urinary Inorganic Phosphorus (Gm./day)	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Serum Cholesterol (mg. %)	Blood NPN (mg. %)	Urine (specific gravity)	Basal Metabolic Rate	Weight (pounds)	Pulse	Treatment
6/10/47	144	..	1.009	+27, +24	111.5	88	
6/11/47	49	1.013	+17, +22	Mercapto-imidazole 60 mg./day
6/16/47	13.7	4.2	49	1.010 1.013 with pitressin	106	76	
6/17/47	+30, +31	72	
6/21/47	.505	72	
6/22/47	.404	72	
6/23/47	.210	13.1	4.2	154	72	
6/24/47	.046	1.011	+29, +15	103.5	72	
6/25/47	.213	.525	.286	1.010	104	72	
6/26/47	.318	.900	.480	1.008	104	72	
6/27/47	.283	.481	.226	72	
6/28/47	.269	.638	.270	104	72	
6/29/47	.287	.460	.214	105	60	
6/30/47	.285	.526	.495	13.1	3.8	181	35	+4, +8	106	60	
7/1/47	.182	.163	Propylthiouracil 300 mg./day
8/4/47	10.3	3.0	254	29	1.009 to 1.014 (1.021 with pitressin)	-13, -13	120.5	40	Propylthiouracil 300 mg./day
8/7/47043	-11, -8	45	Propylthiouracil 300 mg./day
10/10/47	10.3	3.8	183	..	1.009	138	45	Propylthiouracil 300 mg./day
12/13/47	More than 2.5 Gm. daily for eight days preceding this visit	.026	10.4	3.8	160	..	1.020 (16-hour fast) 1.027 (two hours after 1 cc. pitressin)	146.5	45	Propylthiouracil 150 mg./day

minutes and 50 per cent in two hours. The urine was repeatedly sterile. The Sulkowitch test for increased urinary calcium was strongly positive. Several basal metabolic rates ranged from +17 per cent to +31 per cent.

Blood examination revealed a hemoglobin of 58 per cent (9.1 Gm. per cent) and hematocrit of 32 per cent. The white blood count was 5,700 per cu. mm., with polymorphonuclear leukocytes, 81 per cent; lymphocytes, 13 per cent; monocytes, 6 per cent. The blood sedimentation rate was 37/mm. in one hour by the Westergren method.

The serum sodium was 146 mEq./L., chloride, 100 mEq./L. The serum proteins totaled 7.0 G. per 100 cc., with 4.7 Gm. of albumin and 2.3

thorax, vertebrae and lower extremities to be normal. X-rays of the chest and gastrointestinal tract were normal. There was no calcification in the regions of the kidneys or adrenals. The electrocardiogram was within normal limits. Slit lamp examination revealed no band keratitis or abnormalities of the conjunctivae. Other laboratory data are shown in Table I.

On the second day the uptake by the thyroid of radioactive iodide was determined. A maximal accumulation of five to six times normal was found, indicating a hyperfunctioning gland.

Examples of the tests with I^{131} performed on two normal individuals and on the patient described in this report are shown in Figure 1.

The diagnosis of hyperthyroidism was sug-

gested by the weight loss, asthenia, forceful heart beat and the rapid uptake of radioactive iodide by the thyroid gland. Treatment with 2-mercaptoimidazole, 20 mg. every eight hours, was begun on the second hospital day.

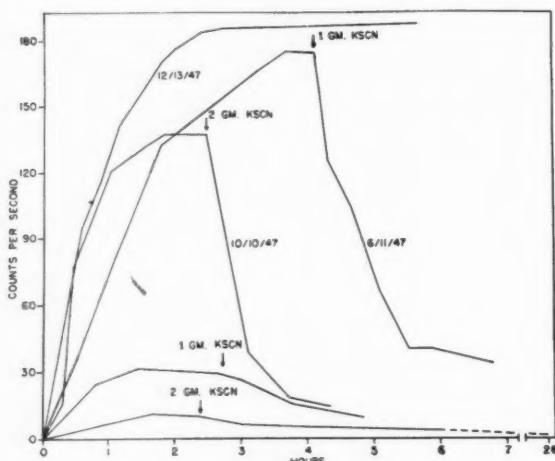


FIG. 1. The iodide accumulation by the thyroid gland in two normal subjects (curves without dates) and in the patient described in this report at the dates indicated. One to two hours before each test, virtually complete inhibition of organic binding of iodine in the thyroid gland was accomplished by administration of 100 mg. of mercaptoimidazole. One hundred microcuries of carrier-free I^{131} were given by mouth in each instance. Serial counts were made by means of a Geiger-Muller counter placed in contact with the skin over the thyroid isthmus. In normal subjects the collection of iodide by the thyroid was relatively slow, with maxima of 35 counts per second or less. The discharge after potassium thiocyanate was also gradual. On the other hand, in the patient the accumulation at the first test (6/11/47) was rapid, with a maximal count of five to six times normal. The loss of iodide after thiocyanate was also abrupt, even more rapid than the uptake. After four months of treatment the maximal count had decreased somewhat. After six months of treatment (12/13/47) the maximal accumulation was slightly higher than originally. This and the thyroid enlargement were presumably reflections of the stimulation of the thyroid by the increased thyrotropin secretion which occurred with the onset of hypothyroidism. The goiter which developed at this time was also probably the result of the same process. Subsequent similar tests were made under these conditions. Almost simultaneously the I^{131} content of the thyroid was determined in absolute terms by means of a sensitive gamma tube 35 cm. from the skin. Comparisons showed that in this patient 1 microcurie I^{131} (1 per cent) in the thyroid was equivalent to 5½ counts per second obtained by counting with the older tube in contact with the skin.

In view of the high serum calcium and the strongly positive Sulkowitch test a low calcium diet was instituted, and the daily urinary excretion of calcium and inorganic phosphorus was

followed. Table 1 presents these values. Despite the low calcium intake the serum calcium remained elevated and the urinary excretion of calcium was high. During this same period the specific gravity of the urine was low, 1.008 to 1.012. At the time when this test period was completed, June 30th, the basal metabolic rate had returned nearly to normal, +4 to +8.

When the patient returned home after twenty-one days in the hospital, his general condition was only slightly improved. The vomiting continued during the first part of his hospital stay so that fluids were administered intravenously on several occasions. He weighed 6 pounds less than on admission; his pulse was slightly decreased from 76 per minute at the beginning of treatment to 60 on discharge. He was placed on a high caloric diet low in calcium and instructed to take propylthiouracil, 100 mg. every eight hours.

The patient was admitted for a second time during August 4-7, 1947. He had noted a marked improvement in his general health during the month since discharge. His strength and appetite had improved and there was no excessive fatigue. He had gained 14½ pounds and was less pale and nervous. He had adhered closely to the low calcium diet and taken propylthiouracil 300 mg. daily. The nocturia had continued however. He had returned to his work on a part-time basis.

Upon physical examination, with the exception of a pulse rate of 40 per minute, there were no abnormalities noted. The thyroid was not palpable.

The blood non-protein nitrogen was 29 mg. per cent; the serum cholesterol was 254 mg. per cent. Urinary phenolsulfonphthalein excretion was 15 per cent in fifteen minutes and 48 per cent in sixty minutes. The total serum proteins were 6.2 Gm. per cent, with albumin 4.3 and globulin 1.9. The hemoglobin was 65 per cent (10.2 Gm. per cent), with a color index of 0.98. The white blood count was 4,300, with polymorphonuclears 45 per cent; lymphocytes, 43 per cent; monocytes, 7 per cent; eosinophiles, 3 per cent; basophiles, 2 per cent. The basal metabolic rates ranged from -8 to -13. The electrocardiogram revealed a sinus bradycardia.

The marked improvement in symptoms, the rise in blood cholesterol and the normal basal metabolic rate were evidence of abatement of hyperthyroidism. The blood non-protein nitrogen and serum calcium had also returned to

normal. The low calcium diet was discontinued and the patient was advised to continue taking propylthiouracil, 100 mg. every eight hours.

The patient was again seen on October 10, 1947. He was asymptomatic at that time except for nocturia, once nightly, which had been noted about half the time. His weight was then 138 pounds, a total gain of 34.5 pounds. He had resumed a normal diet and continued to take propylthiouracil, 300 mg. daily.

Physical examination revealed no abnormalities except a pulse rate of 45 per minute and a slightly enlarged thyroid gland. Laboratory studies revealed a normal urine, with a specific gravity of 1.009 in a random specimen. The blood picture had returned to normal. Additional data are shown in Table 1 and Figure 1.

At the last visit, December 13, 1947, he weighed 146.5 pounds which was normal for him. He had taken 300 mg. of propylthiouracil daily as before. He had recently noted increased sensitivity to cold and increasing tightness of his shirt collars. During the eight days before this visit he had taken 2 quarts of milk daily in addition to his regular diet. On this regimen the nocturia, which had almost completely disappeared, returned with a frequency of about once every other night.

On examination the pulse was 46 per minute. The eyes were slightly puffy and the voice hoarse. The thyroid was moderately enlarged but no bruit or thrill was detectable. The urine was normal and the specific gravity was 1.020 after a fast of sixteen hours. Two hours after 1 cc. pitressin the specific gravity was 1.027. An intravenous pyelogram was entirely normal. Because of the presence of hypothyroidism, the patient was instructed to reduce the dose of propylthiouracil to 150 mg. daily.

COMMENTS

Although the weight loss, muscular weakness, nervousness, palpitation, the forceful heart beat, the elevated basal metabolic rate and lowered serum cholesterol were suggestive of thyrotoxicosis, there were many features against this diagnosis. The weight loss could have been explained by the decreased food intake resulting from repeated vomiting. A low serum cholesterol would be expected with cachexia, particularly in the presence of moderate anemia.

The pulse rate which ranged from 70 to 80 per minute seemed quite unusual in the presence of thyrotoxicosis. However, the statement of the patient that he had always had a slow pulse while in good health was substantiated when it was found to be 45 per minute after two months of treatment. The rate of 70 to 80 per minute therefore represented tachycardia for him.

Recent studies^{1,11-13,15} have shown that hyperplasia of the thyroid is accompanied by an increased collection of radioactive iodide by the gland. In thyrotoxicosis, the most frequent concomitant of hyperplasia, there is a rapid uptake of iodide by the gland, with maximal accumulations above 60 counts per second. Often levels of several times this figure are attained as in the case reported herein. The rate of discharge of the iodide by thiocyanate is comparable to the speed of accumulation. In normal subjects the rate of uptake is slow, with maxima of 35 counts per second or less. The rate of loss of iodide from the gland under the influence of thiocyanate is also gradual and is similar to the collection.

The marked increase over normal in the accumulation of radioactive iodide by the thyroid added strong support to the diagnosis of thyrotoxicosis. It was because of this that proper treatment was instituted promptly in spite of evidence which seemed to make this diagnosis untenable. The subsequent course with antithyroid therapy leaves little doubt that thyrotoxicosis was the primary abnormality although it is probable that it was not the only disease.

The repeated episodes of vomiting, muscular weakness, hypercalcemia, azotemia, impairment of kidney function and increased excretion of calcium in the urine which continued for a time after institution of a low calcium intake at first made the diagnosis of hyperparathyroidism tenable. The normal serum alkaline phosphatase was not considered unusual in the absence of bone changes and also the serum phosphorus was normal. The reversion to normal of the high serum calcium and the dramatic improvement in the other symptoms while

under antithyroid treatment made it improbable that this disease was present.

Addison's disease was also suggested by the vomiting, weakness, tanned skin, weight loss, hypotension, azotemia and fixed urinary specific gravity. The normal-sized heart with a forceful beat, the warm skin and the elevated basal metabolic rate were against this diagnosis. The pigmentation of the skin could be adequately explained by recent exposure to the sun; there was no pigmentation of the mucous membranes. The levels of sodium, potassium and chloride in the serum were normal. The lasting improvement without specific therapy for Addison's disease excluded this disorder. The changes in calcium metabolism could not be explained on the basis of adrenal cortical hypofunction.

By calculation from the food history the intake of calcium, which had approximated 1.4 Gm. per day prior to the first admission, was higher than average. It was suggested that the whole picture might be explained on this basis, with the hypercalcemia resulting from the inability of the kidneys to excrete the excess calcium adequately. The presence of kidney disease, either chronic glomerulo- or pyelonephritis, was postulated. However, the calcium intake was not greatly in excess of that taken by many individuals. There were no corneal or conjunctival lesions such as have been described in individuals with hypercalcemia of long duration.¹⁶ If the syndrome were on this basis, it would be expected that the change to a low intake would result in a significant decrease in the serum calcium or in the urinary calcium excretion. This did not occur in nine days. (Table 1.) Instead, however, the change to normal values occurred over a period of several weeks. This interval would probably be required for the reversion of such metabolic disturbances due to thyrotoxicosis even under adequate treatment with an antithyroid drug.

The evidence for renal disease consisted of isosthenuria, impaired urinary excretion of phenolsulfonphthalein, slight azotemia

and moderate anemia. The urine was sterile, contained slight to moderate amounts of albumin, a few white and red blood cells and occasional hyaline and granular casts. Improvement with treatment was accompanied by return to normal of the blood non-protein nitrogen and an increased ability of the kidneys to concentrate the urine. The type of renal disturbance is not known. The presence of kidney dysfunction following acute alkalosis was considered; the only evidence for this latter was a plasma carbon dioxide capacity of 69 volumes per cent. In the absence of a history of ingestion of alkalies the repeated vomiting, with perhaps accompanying dehydration, remained a possible etiologic factor; the normal plasma chlorides made this unlikely. However, since both the acute alkalosis and renal damage may be transient and reversible, it is possible that the former may have been present in our patient before admission. He had no evidence of residual kidney disease after recovery from thyrotoxicosis.

Other common causes of hypercalcemia were not present. The patient had not received medication containing vitamin D so the intake of this substance was not excessive. The serum proteins were normal. The four normal subjects studied by Dietrick, Whedon and Shorr⁴ exhibited increased urinary and fecal calcium excretion during six to seven-week periods of complete immobilization produced by plaster casts extending from the umbilicus to the toes. Slight elevation of the serum calcium levels occurred during the latter part of the period of immobilization and early in the recovery phase, with a maximum rise of 1.8 mg. per cent. The patient described herein was never confined to bed for longer than one or two days at a time and never without bathroom privileges; his activity was not restricted during recumbency. Thus it seemed unlikely that bed rest was an important factor in bringing about the changes in calcium metabolism in our patient.

The vomiting, which was such a prominent symptom, was probably the result of

the elevation of serum calcium. Although an increased urinary and fecal excretion of calcium occurs frequently in thyrotoxicosis,^{2,9} hypercalcemia is uncommon. In the great majority of cases of thyrotoxicosis the levels of calcium in the serum are normal. However, in the review of Poppel et al.⁹ cases were cited with serum calcium levels of 12.1 mg. per cent (E. M.), 12.4 mg. per cent (M. C.) and 14 mg. per cent (L. M.) while on low calcium intakes. On the other hand, Robertson¹⁰ considered the average levels of 9.71 mg. per cent (range 9.1 to 10.8) in the group of fourteen thyrotoxic patients studied by him to be significantly lower than the average of 10.39 mg. per cent for normal persons (range 9.9 to 11.1).

As further evidence for frequent disturbances in calcium metabolism in thyrotoxicosis, Golden and Abbott⁵ found roentgenologic evidence of significant osteoporosis in 22 per cent of 110 cases. Since only chest films were available in sixty-three instances, the true incidence was probably higher than this. (Of nine patients in whom complete studies were available six had decalcification.) The x-ray picture of metastatic cancer and what was clinically termed "arthritis" have been described with osteoporosis due to thyrotoxicosis.^{8,9} Several instances of spontaneous fractures due to such osteoporosis have been reported.^{3,6,14} The skeletal system of the patient described here appeared to be normal by x-ray.

Although at times there may be a resemblance between the clinical picture due to thyrotoxicosis and to hyperparathyroidism, they are usually easily distinguishable. Six instances of the simultaneous occurrence of these two diseases in the same person, three of which were confirmed at operation, have been reviewed by Miller and Evans.⁷

In our patient, because of the hypercalcemia and associated renal dysfunction, the diagnosis of co-existing hyperparathyroidism could not be lightly dismissed even with the normal serum phosphorus and alkaline phosphatase levels. After com-

plete response to antithyroid mediation, however, it could be ruled out with certainty.

In the usual case of thyrotoxicosis the kidneys are able to excrete the increased amounts of calcium and to maintain a normal serum calcium. In our patient an explanation of the situation might be that the kidneys, while able to excrete more than normal amounts, because of impaired function could not clear enough calcium to prevent hypercalcemia. This, of course, presumes that the primary event was an increased mobilization of calcium from the bones as a result of the excessive catabolism generally occurring in thyrotoxicosis.² This explanation would not be compatible with other theories as to the cause of the excessive excretion of calcium in this disease.

SUMMARY

A patient with thyrotoxicosis exhibited recurrent vomiting, a normal heart rate, azotemia, a fixed urinary specific gravity and hypercalcemia with increased calcium excretion in the urine. Strong evidence for the correct diagnosis was provided by the elevated uptake of radioactive iodide by the thyroid gland. While under treatment with antithyroid drugs alone, he attained a state of normal health, including normal kidney function. The correction of the abnormalities while under specific therapy for thyrotoxicosis made it unlikely that hyperparathyroidism co-existed and thus confirmed the original diagnosis.

Acknowledgment: We are grateful to Dr. E. B. Astwood for helpful suggestions in the preparation of this manuscript.

ADDENDUM

Since this manuscript was submitted, further information has become available. At the patient's last visit, November 24, 1948, three months after all antithyroid medication had been discontinued, he was asymptomatic. He weighed 170 pounds. The thyroid was barely palpable. The heart rate was 45 beats per minute. There were no other physical abnormalities. The urine was normal, with a specific gravity of 1.016

in the random specimen. The serum calcium was 10.2 mg. per cent, phosphorus 3.2 mg. per cent, cholesterol 178 mg. per cent and alkaline phosphatase 1.8 Bodansky units per 100 cc. The thyroid radioactive iodine uptake was 14.3 counts per second, or 2.6 per cent, values which were within normal limits.

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Influenzal Meningitis in Adults*

Report of a Case Complicating the Nephrotic Syndrome

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ALTHOUGH *Hemophilus influenzae* is a common cause of acute, purulent meningitis in children, this type of meningeal infection has rarely been encountered in adults. A review of the literature revealed only thirty reports dealing with this disease in persons twenty or more years of age. Analysis of the reports indicated that the disease in the older age groups differed in some respects from that in the very young. It seemed of interest, therefore, to report the following case of *Hemophilus influenzae*, type B, meningitis occurring in a woman of forty-eight and to emphasize some of the characteristics of the infection. A unique feature of the case is the fact that the meningitis occurred as a complication of the nephrotic syndrome.

CASE REPORT

A forty-eight year old, white female school teacher complaining of left anterior chest pain of two days' duration was admitted to The Mount Sinai Hospital, New York, on October 25, 1947.

Two weeks before admission she developed a severe upper respiratory infection, associated with a low grade fever and a dry cough. The fever subsided in a few days but the cough persisted and with the onset of the chest pain it became productive of rusty sputum and there was a temperature elevation to 101°F. (rectally).

Four months prior to the onset of her present illness she developed bilateral pitting edema of the legs. The blood pressure was 120/80. Urinalysis at that time showed 4 plus albuminuria with many hyaline casts. The serum protein level was 3.6 Gm. per cent and the serum cholesterol was 318 mg. per cent. On the basis of these findings a diagnosis of the nephrotic stage of chronic glomerulonephritis was made.

She was placed on a high protein, low salt diet and was given thyroid extract (1 gr. three times daily), vitamin B complex and ammonium chloride (2 Gm. three times daily). On this regimen she felt well and had only minimal edema of the legs. The albuminuria persisted without change.

On admission to the hospital examination revealed a well nourished, well developed, acutely ill, white female of forty-eight, with marked respiratory distress. The rectal temperature was 101°F., pulse rate was 100 and the respiratory rate was 32. There was a well marked arcus senilis and the pupils were contracted. The neck veins were distended. There was some splinting of the left thoracic cage. The percussion note was impaired over the left chest posteriorly and in the left axilla. Bronchial breathing was heard over the left lower lobe and there was a grating friction rub in the left axilla. There were fine, moist inspiratory rales at the base of the left lung. The heart sounds were good; a soft systolic murmur was heard only at the apex. The blood pressure was 108/70. The abdomen was slightly distended. The liver, spleen and kidneys were not felt. There were no abnormalities on rectal or vaginal examination. Examination of the extremities revealed mild edema of both ankles. The reflexes were normal.

The specific gravity of the urine was 1.012. It contained no sugar but there was a large amount of albumin present, with many waxy, hyaline and granular casts and two or three white blood cells as well as two or three red blood cells per high power field. The hemoglobin concentration of the blood was 9.6 Gm.; the red blood cell count was 3.39 million; the white blood cell count was 9,350 with 2 per cent myelocytes, 65 per cent non-segmented polymorphonuclear neutrophiles, 14 per cent segmented polymorphonuclear neutrophiles, 16 per cent lymphocytes and 3 per cent monocytes.

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The erythrocyte sedimentation rate was 135 mm. in one hour (Westergren). The blood urea nitrogen was 7 mg. per cent.

A typing of the sputum for pneumococci was negative. Sputum culture revealed *Streptococcus viridans* (alpha) and *Streptococcus anhemolyticus* (gamma). Roentgen examination of the chest at the bedside showed pneumonic infiltrations occupying most of the left lung. The provisional diagnosis was severe lobar pneumonia with the nephrotic syndrome.

The patient was given injections of crystalline penicillin G (100,000 units every three hours) intramuscularly. During the first twenty-four hours she became markedly stuporous and her temperature rose to 103.2°F. The pulse was 128 and the respiration was 36. She was given a 500 cc. blood transfusion and the penicillin was increased to 200,000 units every three hours. Despite these measures the stupor continued. The picture was interpreted as one of profound toxemia due to an overwhelming infection in a nephrotic subject.

On the third hospital day improvement was noted. The patient was now rational and cooperative. Her rectal temperature had dropped to 100°F. There were no meningeal signs. Another blood transfusion was administered and, in addition, she was given amigen solution intravenously (1,000 cc.) in an attempt to combat hypo-amino-acidemia. Although the organisms causing the infection were still unknown, it was believed that there had been a favorable response to therapy. That evening, however, her condition became worse. Her temperature rose to 104°F., with a pulse rate of only 66. The blood pressure was now 170/70. The patient appeared drowsy, complained of severe headache and vomited. Lumbar puncture revealed cloudy spinal fluid containing 2,200 cells per cu. mm., with a predominance of polymorphonuclear leukocytes. The Pandy reaction was 4 plus. No organisms were seen on direct smear of the spinal fluid. Because of meningitis, the patient was given 4 Gm. of sodium sulfadiazine intravenously and this was followed by 1 Gm. every four hours intravenously. The dose of penicillin was increased to 400,000 units intramuscularly every two hours and 10,000 units of penicillin were given intrathecally.

On the fourth hospital day she relapsed into a semistupor. Examination of the ears, nose and throat for foci of primary infection revealed no active disease although the right antrum was

dark to transillumination. Later that day *H. influenzae*, type B, was identified in the blood culture taken on admission and was also found in a culture of the sputum and in the cerebrospinal fluid. Lumbar puncture was repeated and 100 mg. of streptomycin calcium chloride complex were injected intrathecally. In addition, 0.5 Gm. of streptomycin was given intramuscularly every six hours. At this time therapy consisted of sodium sulfadiazine intravenously, streptomycin intramuscularly and intrathecally and penicillin intramuscularly.

By the seventh day general improvement was clearly apparent. The patient became alert, responsive and completely rational. The neck signs were almost gone. She was able to take sulfadiazine and fluids by mouth. The spinal fluid culture was negative and concentration of the sugar had risen to 55 mg. per cent from 15 mg. per cent. Roentgen examination of the chest revealed fluid at the left base which partially obscured a pulmonary infiltration.

By the tenth day the temperature had fallen to 98.6°F. Use of sulfadiazine and penicillin was discontinued. Although the cough persisted, the pulmonary signs had definitely cleared. Spinal fluid glucose concentration was 70 mg. per cent. Blood urea nitrogen was 9 mg. per cent, cholesterol was 440 mg. per cent, total protein was 4.6 Gm. per cent, with albumin 2.7 Gm. per cent and globulin 1.9 Gm. per cent.

By the twelfth day she was out of bed in a chair and complained only of a slight headache. The signs in the chest had almost completely cleared but x-ray examination of the chest still revealed infiltration in the lower two-thirds of the left lung. On the fourteenth day streptomycin was discontinued.

The remainder of the hospital stay was uneventful. The patient complained of mild frontal headache from time to time but the temperature remained normal. On attempting to walk she was unsteady and staggered slightly. An otologic consultant was of the opinion that slight impairment of vestibular function was present. Analysis of the blood now revealed a total protein of 5.3 Gm. per cent, with albumin 2.9 Gm. per cent and globulin 2.4 Gm. per cent, cholesterol 500 mg. per cent, blood urea nitrogen 17 mg. per cent. Roentgen examination three weeks after admission still revealed some infiltration in the left lower lobe of the lung. This lobe was smaller than previously noted and its appearance suggested some degree of

atelectasis. The patient was discharged with no residual meningeal or pulmonary findings twenty-four days after admission.

COMMENT

Meningitis due to *H. influenzae* is essentially a disease of early childhood.

tributable to a humoral antibody. Moreover, they pointed out that between the ages of two months and three years this bactericidal power is almost completely lacking from the human blood and that after three years it increases, reaching its maximum in adults.

TABLE I

ESSENTIAL CLINICAL AND LABORATORY FINDINGS IN SIXTEEN CASES OF INFLUENZAL MENINGITIS IN ADULTS

Cases	Authors	Age	Sex	Type of Onset	Primary or Secondary	Cultures		Complications of Meningitis	Treatment	Outcome
						Spinal Fluid	Blood			
1	Cohoe ²	33	M	Head injury two weeks prior	?S	Smear and culture positive	Negative	None	Non-specific lumbar puncture	Recovery
2	Needles ³	29	M	Tooth extracted four days prior	?S	Culture positive	None	None	Non-specific	Recovery
3	Dyke ⁴	29	M	Ear infection preceding onset	S	Smear and culture positive	None	None	Non-specific	Recovery
4	Neal et al. ⁵	28	M	Six-day history of headache and vomiting	P	Smear and culture positive	Negative	Deafness	Antimeningeal and antiinfluenzal serum	Recovery
5	Neal et al. ⁵	38	M	Followed severe head injury	S	Culture positive	None	None	Antimeningeal and antiinfluenzal serum	Recovery
6	Watson-Williams ¹⁴	46	F	Followed ear infection of seven days	S	Smear and culture positive	None	None	Non-specific intravenous silver	Recovery
7	Teggart ⁶	60	M	Two-week history of lethargy, headache, etc.	P	Culture negative; smear, small gram-negative bacteria	None	None	Soluseptasine	Recovery
8	Mulder ⁷	28	M	Tonsillitis for five days	S	Culture positive	None	None	Non-specific	Death
9	Pellegrini ⁸	58	M	Headache for five days	P	Smear and culture positive	None	None	Sulfonamides	Recovery
10	Neal et al. ⁹	51	M	Headache	P	Culture positive	Negative	None	Sulfapyridine, sulfanilamide, serum	Recovery
11	Neal et al. ⁹	35	M	Followed submucous resection and ethmoidectomy	S	Culture positive	Negative	None	Sulfapyridine, serum	Recovery
12	Neal et al. ⁹	22	M		P	Culture positive	Negative	None	Sulfapyridine, serum	Recovery
13	Harold ¹⁰	59	M	Three-day history of headache	P	Culture positive	None	None	Sulfapyridine	Recovery
14	Mutch ¹¹	30	M	Two-week history of headache	P	Culture negative; smear, gram-negative bacillus	None	None	Sulfonamides	Recovery
15	Baumgartner and Nuzum ¹²	39	F	Ear infection of one week	S	Culture positive	None	None	Sulfanilamide	Recovery
16	Becker and Spingarn	48	F	Upper respiratory infection, pneumonia, nephrotic syndrome	S	Culture positive	Positive	None	Penicillin, sulfadiazine, streptomycin	Recovery

Most of the cases occur during the first three years of life. The incidence drops sharply from the fourth to the tenth years and the disease is very infrequently seen after the age of twenty. The relation of age to the incidence of this infection has been of interest to immunologists. Fothergill and Wright¹ demonstrated that human blood was highly bactericidal for influenza bacilli and that the bactericidal power is at-

Since Cohoe's² first report of a case of *H. influenzae* meningitis in an adult, we were able to find reports of twenty-nine additional cases. The essential clinical features of fifteen of the cases that were reported in sufficient detail have been tabulated (Table I) to indicate some of the characteristics of the disease in the adult.

Although in children influenzal meningitis occurs with equal frequency in both

males and females, in adults thirteen of the patients were males. This sex difference is probably a fortuitous one due to the small series. In children influenzal meningitis has been regarded generally as a primary infection.^{7,12,13} In the group of adults four were secondary to a severe upper respiratory infection such as acute tonsillitis or acute otitis media.^{4,7,14,15} One case occurred following a submucous resection and an ethmoidectomy.⁹ Two cases occurred after head injuries^{2,5} and one followed a tooth extraction.³ Only seven (46 per cent) of the cases were regarded as primary meningeal infections.^{5,6,8-11} In our case cultures of the sputum, blood and spinal fluid all yielded *H. influenzae*, type B. Apparently this is the first reported adult case in which meningitis followed primary pneumonia due to this organism.

In children influenzal meningitis has been attended by a case fatality rate of over 90 per cent. Since 1937, use of anti-influenzal serum, sulfonamides, penicillin and finally, streptomycin, singly and in combination, has reduced this to a low level.^{17,18} However, in the group of adult cases, among eight reported prior to 1940 and the patients treated with a variety of non-specific measures, there was only one death. There were no deaths in seven other patients whose cases were reported since 1940 who were treated with sulfonamides and serum. Neurologic complications due to residual damage to brain and cranial nerves were noted in only one patient⁵ although these have been common among children who survived the infection. These findings suggest that the prognosis of the disease in adults is better than in children.

The occurrence of the nephrotic syndrome complicated by *H. influenzae* pneumonia and meningitis in an adult has not been previously recorded. It is well known that nephrotic subjects are very susceptible to bacterial infections due to pneumococci and streptococci which may prove fatal. In fact, when our patient was first seen with pneumonia, a pneumococcal or streptococcal infection was diagnosed because

of the nephrotic background. Penicillin therapy was therefore instituted. The relationship of the nephrotic syndrome to the onset of the infection is one of some interest since the former state may have impaired the immunologic defense of the patient. In the nephrotic syndrome hypoproteinemia is associated with a definite decrease in the antistreptolysin titer in children.¹⁹ Although we have no evidence regarding the bactericidal power of the blood for influenza bacilli in adults with the nephrotic syndrome, it is possible that this was reduced or absent as it is in infants. Consequently, the nephrotic state may have been an important factor favoring the onset of meningitis at an age when the disease is uncommon.

SUMMARY

1. A case of *Hemophilus influenzae*, type B, meningitis and pneumonia complicating the nephrotic syndrome is reported in a woman of forty-eight.
2. The overwhelming infection responded promptly to use of intrathecal and intramuscular streptomycin in the usual therapeutic dosages.
3. A review of the literature pertaining to *H. influenzae* meningitis in adults revealed features which distinguish it from the disease as it occurs in infants and children.

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Endocarditis Due to *Hemophilus Influenzae*^{*}

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BACTERIAL endocarditis due to a gram-negative organism is relatively rare and involves therapeutic problems of considerable interest. Therefore, we are reporting two cases of *Hemophilus influenzae* endocarditis, both resulting in recovery. One of these patients was cured by streptomycin and it is probable that the recovery of the other is attributable to streptomycin.

CASE REPORTS

CASE 1. (Fig. 1.) Mrs. E. B., (No. 558876)† a thirty-two year old housewife, entered the hospital on January 2, 1947, because of a nightly fever of two months' duration. At the age of five, twenty-seven years previously, she had had severe migrating polyarthritis, diagnosed as rheumatic fever, which had left her with a "bad heart." Her only symptom through the years, however, was slight dyspnea on exertion.

About fifteen months before entry she began to lose weight and a few months later her appetite failed. She had lost about 40 pounds at the time of admission. Two months before entry she developed a fever of 102°F. and thereafter every evening ran a temperature between 99 and 102°F. During the first febrile month she was given penicillin-in-oil injections daily for two weeks. During the second month she was given a second course of 2 injections daily for one week. This therapy had no effect on the fever and the patient finally sought hospitalization.

Physical examination revealed a poorly nourished young woman with petechiae visible in the conjunctivae and on the palate. The chest was clear. The heart was not enlarged and exhibited a normal rhythm at a rate of 80. There was a systolic thrill over the aortic area

and a diastolic thrill at the apex. Systolic and diastolic murmurs were audible at both the base and apex, consistent with mitral and aortic valvular disease. Blood pressure was 120/40–0. The spleen was palpable 1 cm. below the left costal margin and there was moderate clubbing of the fingers.

Laboratory data revealed the following: The white blood count averaged 7,000 cells per cu. mm., the differential count being normal; hemoglobin remained at about 10 Gm. per cent; the sedimentation rate was 1.4 mm. per minute. Repeated urinalyses were negative. X-ray of the chest showed some prominence of the left ventricle but was otherwise not remarkable. The electrocardiogram was normal.

During the hospital course the patient ran an oscillating fever, the temperature usually being normal in the morning and as high as 103.8°F. by late afternoon. After three weeks a definite bacteriologic diagnosis had not been made, despite venous blood cultures twice daily, an arterial blood culture and a sternal marrow culture. Nevertheless, it was decided to start the patient on penicillin, one million units daily by constant intramuscular drip, as a therapeutic trial. During the eight days in which the ineffectuality of this treatment became apparent, an organism was recovered from the previous blood cultures and identified as *H. influenzae*. It grew too slowly to allow determination of penicillin sensitivity but was inhibited by streptomycin in a concentration of 2 units (0.002 mg.) per cc. Consequently, penicillin was stopped and streptomycin was begun at a dosage of 0.4 Gm. every four hours, or 2.4 Gm. per day. Although the streptomycin serum level at this dosage was over 16 units per cc., there was not an immediate fall in temperature to normal and it was feared that the resistance of the organism to streptomycin was rapidly increasing. The dose was therefore increased on the fourth day to 0.7 Gm. every four hours, or 4.2 Gm. per day. This gave a serum level of over 32 units per cc., but the

† This case has previously been noted elsewhere as a progress report¹ and was also briefly mentioned by Paul, Bland and White.²

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temperature continued to swing as high as 101°F. On the eighth day of streptomycin therapy the temperature reached 103°F. and the patient developed a generalized, pruritic, erythematous rash. Benadryl and, subsequently, pyribenzamine were administered; with the

She is able to get along under most conditions, except when walking on an uneven surface in the dark.

Comment. This case represents one of the earlier successful attempts to cure

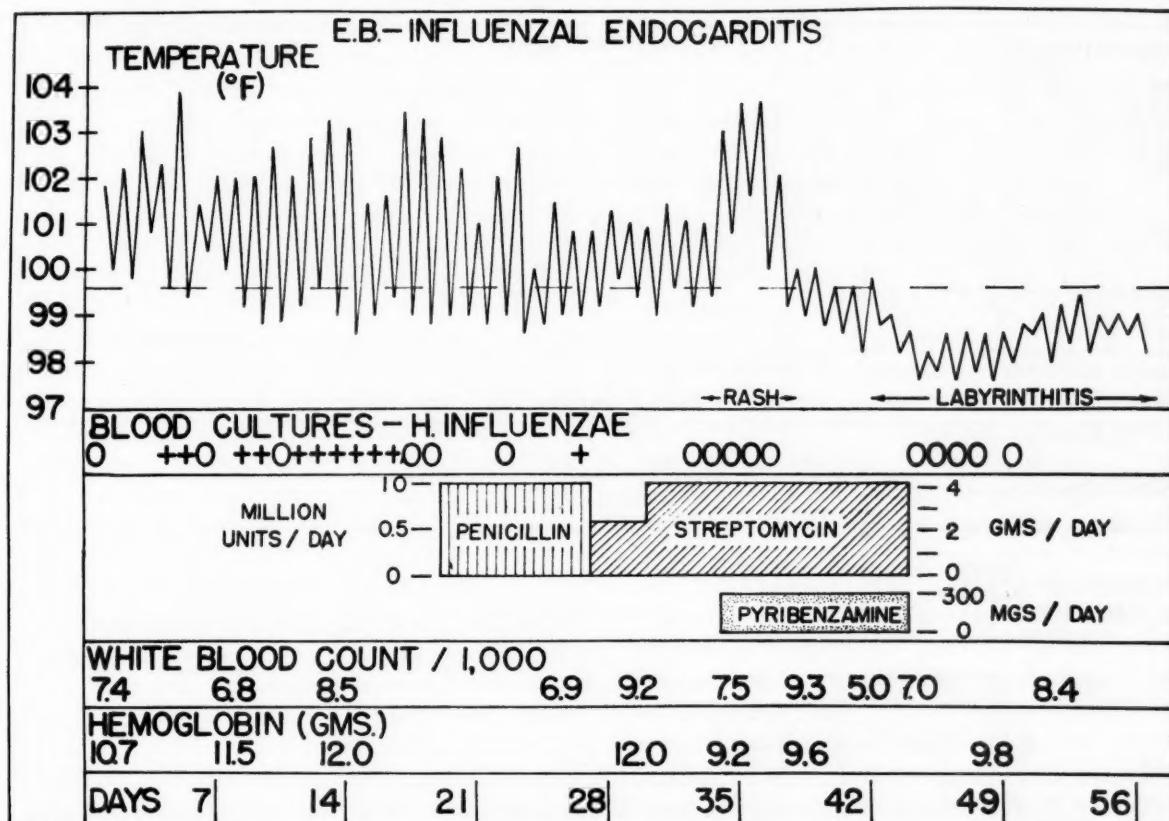


FIG. 1. Chart of the clinical course in Case 1. Note the positive blood culture during penicillin treatment.

latter there was prompt disappearance of the dermatitis and a fall in the temperature to a normal level. On the tenth day of streptomycin administration she first complained of slight dizziness and by the sixteenth day had developed nausea, vomiting and true vertigo. As a consequence streptomycin was stopped on the seventeenth day of treatment, at which time the patient had been afebrile for five days. She remained afebrile for the following two weeks and was discharged from the hospital still suffering from marked vertigo. Although a blood culture during penicillin treatment had been positive, all cultures during and after streptomycin treatment were negative.

At present, more than one year later, she is in good health without evidence of relapse or re-infection. She still has no labyrinthine function but has adapted herself quite well to this loss.

subacute bacterial endocarditis due to a gram-negative organism by means of streptomycin. Several problems presented themselves, first of which was the great difficulty in determining the nature of the infecting organism. The resulting delay, however, gave us an opportunity to observe the inefficacy of penicillin in the dosage administered.

Second, there was the problem of estimating the dosage of streptomycin necessary to effect a cure when the organism was known to be extremely sensitive *in vitro*. The rather large dose finally agreed upon reflected our fear that resistance to the drug might develop rapidly. We could not afford to lose the opportunity to cure this patient by erring on the side of inadequate dosage.

The third problem concerned the complications of streptomycin therapy—fever, dermatitis and labyrinthitis. It is of interest that although the febrile reaction and the skin rash promptly disappeared under treatment with antihistaminic drugs they

entered the hospital on November 10, 1947, because of ten days of fever, chills, weakness and dizziness.

At the age of four he had had an illness diagnosed as rheumatic fever; there were recurrences at eight and twelve. By the age of

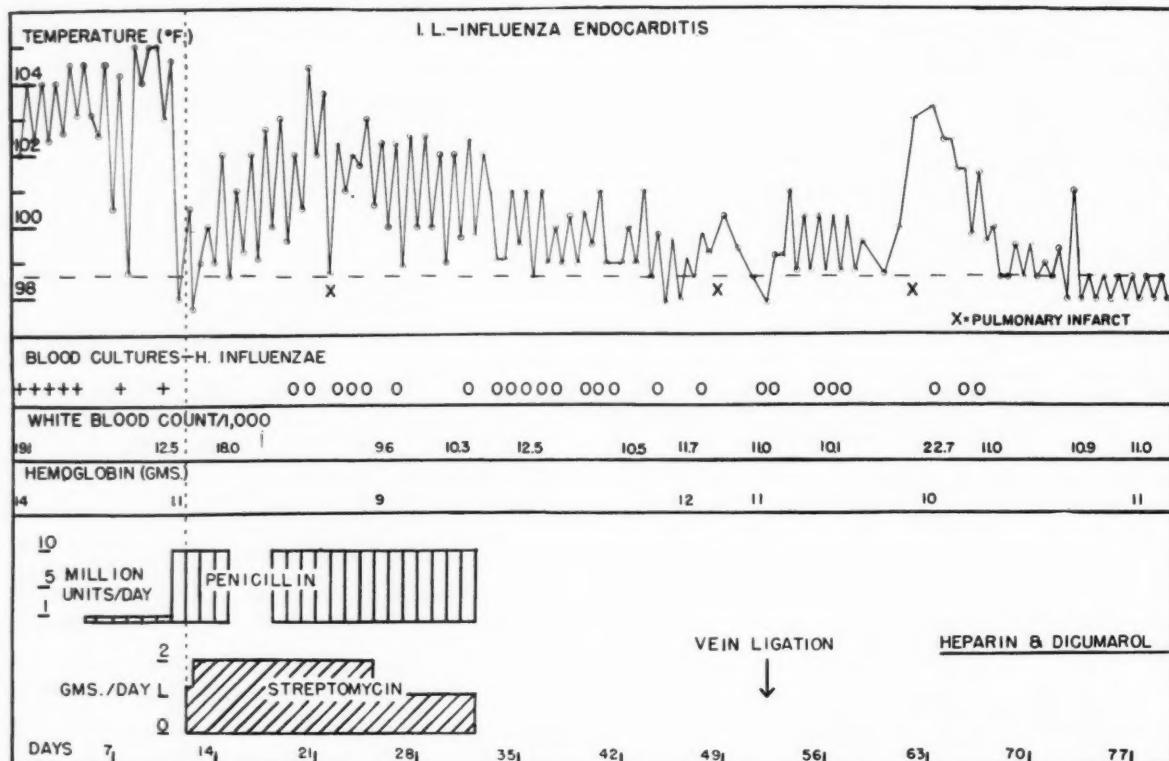


FIG. 2. Chart of the clinical course in Case II. Note the apparent response to the increased dosage of penicillin.

had no effect whatever on the development and progression of labyrinthitis. Streptomycin was continued in the face of increasing vertigo, nausea and vomiting, with full knowledge that the labyrinths were being sacrificed in an effort to cure a uniformly fatal disease. In retrospect, it may well be argued that a similar cure could have been obtained by using a smaller dose of streptomycin, thereby greatly reducing the likelihood of labyrinthitis. It is impossible to answer this question in any individual case but we believe the large dosage was entirely justified here. At any rate the loss of labyrinthine function has not seriously interfered with the patient's normal activities.

CASE II. (Fig. 2.) Mr. I. L. (No. 55578) was a twenty-five year old draughtsman who

seventeen a moderately loud, apical systolic murmur and a faint aortic diastolic murmur had appeared. There were no further episodes of rheumatic fever and he led a sedentary life without symptoms.

In August, 1947 he had an illness characterized by malaise, headache and moderately high fever. There were no localizing complaints. The symptoms subsided in about two weeks and were attributed to "grippe." In November, however, quite suddenly he began to have shaking chills, a fever to 103°F. by mouth, dizziness, weakness and occasional vomiting. He had noticed no skin rash or chest pain; there had been no preceding oral surgery. After ten days of these symptoms he entered the hospital.

On admission he did not appear particularly ill, but his temperature was 103.5°F. by rectum and his pulse was 120, with a regular rhythm. Otherwise his condition did not differ materially from that noted in the clinic in previous

years. There were an aortic diastolic murmur and a questionable mitral diastolic murmur. There was one questionable petechial hemorrhage inside the lower lip; there was no clubbing of the fingers; the spleen was barely palpable.

Laboratory data revealed the following: The white blood count was 20,000 cells per cu. mm., with 80 per cent neutrophiles, 7 per cent lymphocytes, 12 per cent monocytes, and 1 per cent eosinophiles. The hemoglobin was 14 Gm. per cent. The urine showed a specific gravity as high as 1.026, no albumin and at most 3 to 5 red blood cells per high power field in the spun sediment. A chest film and electrocardiogram were within normal limits.

The temperature remained between 102 and 104°F. by rectum. On the fifth hospital day, in the absence of a bacteriologic diagnosis but on strong suspicion of bacterial endocarditis, treatment was begun with one million units of penicillin per day by constant intramuscular drip in the anterior thigh. A level of at least 5 units of penicillin per cc. of serum was maintained. After six days of treatment the fever remained high and an alarming lethargy appeared. The hemoglobin had dropped from 14 to 11 Gm. per cent. The dosage of penicillin was increased to ten million units per day, bringing the serum level to at least 10 units per cc. There was a definite clinical response to the increased dosage within twelve hours. The temperature dropped from 104°F. to normal and there was a marked improvement in the patient's alertness and sense of well being.

At the same time, however, it was learned that *H. influenzae* had been identified in all seven of the blood cultures taken since the patient's admission; two of these had been drawn while penicillin was being given at the rate of one million units a day. The organism grew in rough, compact colonies and could not be typed with the existing antisera. *In vitro* it was inhibited by a streptomycin concentration of 1 unit (0.001 mg.) per cc. but grew in a penicillin concentration of 66 units per cc. As soon as the organism was known and before sensitivities were available streptomycin was added at the rate of 2 Gm. a day in divided intramuscular doses of 0.25 Gm. every three hours. The serum level of streptomycin, measured just before administration of one of these doses, was 32 units per cc., or at least thirty-two times the level required to inhibit growth *in vitro*. Penicillin was discontinued for three days, but when the

temperature began to reach daily peaks of 102°F. it was resumed. Although the organism was now known to be one generally considered insensitive to penicillin, the previous response to high penicillin dosage had seemed definite. Streptomycin was given for three weeks, at the rate of 2 Gm. a day for two weeks and 1 Gm. a day for one week; a total of 33.25 Gm. was administered. Penicillin was given by constant drip for a total of twenty-five days, the total dose being 187,000,000 units. The temperature continued to rise to 102°F. daily while chemotherapy was continued; it gradually fell to normal in the two weeks following cessation of treatment. There was no other suggestion of drug sensitivity nor was there evidence of streptomycin toxicity by ordinary clinical standards. He was given several blood transfusions during the course of treatment.

He continued to feel well, in general, but three episodes of pulmonary infarction complicated his recovery. The first occurred while he was receiving chemotherapy and while he was on complete bed rest because of the constant intramuscular drip in the anterior thigh. Pain and tenderness at the injection site were considerable although clinically there was no area of venous thrombosis. Because of the possible danger of subarachnoid hemorrhage, anticoagulant therapy was avoided while the possibility of active endocarditis was present; venous ligation was not performed because of the difficulties likely to follow the intramuscular drip. The second episode occurred three weeks after the cessation of chemotherapy during which time the patient was ambulatory. It was promptly treated by bilateral superficial femoral vein ligation, only to be followed by a third large pulmonary infarct two weeks later. After three weeks of anticoagulant therapy (heparin and dicumarol) he appeared perfectly well, an elevated sedimentation rate being the only abnormal finding. He was finally discharged from the hospital on January 30, 1948.

At present, six months after chemotherapy was stopped, all evidence points to recovery from bacterial endocarditis. All blood cultures have been negative since streptomycin was begun. The sedimentation rate, white blood count and temperature all remain normal. The patient has gained weight and is back at work. A slight aortic diastolic murmur is the only cardiac abnormality discernible. There have been no further episodes of pulmonary infarction.

Comment. It seems probable that streptomycin was the agent responsible for the patient's recovery. His critical condition demanded the continuation of penicillin as well as streptomycin. This was unfortunate for the nicety of the clinical experiment but certain evidence suggests that penicillin did not contribute to his recovery: (1) There were several positive blood cultures after starting therapy with one million units of penicillin per day. (2) The *in vitro* resistance of the organism to penicillin was great (it was not inhibited by 66 units per cc.) and blood levels of penicillin actually obtained did not approach the level which this resistance would seem to require.

On the other hand, there did appear to be a definite clinical response to the institution of heavy penicillin dosage, and it was largely on the basis of this apparent response that penicillin was continued. It is quite possible that the apparent "response" was merely a coincidental variation in the underlying disease. No final conclusions can be drawn since streptomycin was started on the day following the increase in penicillin dosage.

The recurrent pulmonary emboli were a serious complication although not one directly related to the problem of chemotherapy. Their source remained uncertain. The heart itself was a possibility, although an unlikely one, since there was no evidence of a tricuspid or an interventricular septal lesion. There was also no definite evidence to incriminate the veins of the legs but statistically they were the most likely source of emboli. Some question must be raised as to the advisability of using the muscles of the legs to receive a constant intramuscular infusion for long periods during which time bed rest is unavoidable.

COMMENTS

In addition to the present cases nine instances of recovery from bacterial endocarditis due to gram-negative organisms have been reported.³⁻⁷ In three of these the responsible organism was an unclassified gram-negative bacillus; in the other six

either *H. influenzae* or *H. parainfluenzae* was recovered. Streptomycin was used in the treatment of two of the *Hemophilus* patients, although in one of them⁶ the role of streptomycin cannot be determined from the information furnished; in the other,⁷ its role is unequivocal. In the first case presented herein recovery was undoubtedly due to streptomycin; in the second, streptomycin was probably responsible for recovery.

Thus the evidence, although not great in bulk, indicates that streptomycin is highly effective in treating *Hemophilus* endocarditis and is as effective here as in other infections due to these organisms. In fact, three of the four patient's cases now reported (one noted by Hunter,⁶ that of Massell et al.⁷ and the present Case II) recovered with a relatively moderate dosage of 2 Gm. per day. None of the three showed evidence of permanent eighth nerve injury. We were unable to find any reports of streptomycin failure in *Hemophilus* endocarditis.

It is worth remembering, however, that the sulfonamides and penicillin may at times be of use in *H. influenzae* infections. The possible effectiveness of penicillin was suggested in Case II. Although penicillin was at first considered to have no effect on *H. influenzae*, there is now a considerable amount of evidence to show that some strains may be strikingly sensitive, both *in vitro* and in meningeal infections.^{8,9} In general, clinical success was associated with high *in vitro* sensitivity.

It has been pointed out by Dienes,¹⁰ however, that most strains of *H. influenzae* which have apparently been inhibited by penicillin will eventually show growth after prolonged incubation even though concentrations as high as 1,000 units per cc. have been used. Hence, penicillin sensitivity as ordinarily determined may be a guide only to the susceptibility of the less resistant organisms in a given strain. It is entirely possible that here and elsewhere penicillin and streptomycin may act synergistically. This sort of "chemotherapeutic crossfire" has already been suggested by Hunter.⁶

SUMMARY

1. Streptomycin is effective in the treatment of bacterial endocarditis due to *Hemophilus influenzae*. It was responsible for recovery in one of the cases presented and probably responsible in the other.

2. Use of other chemotherapeutic agents, particularly penicillin, should not be overlooked in the treatment of *Hemophilus* infections.

Acknowledgments: We would like to express our indebtedness to Dr. Edward F. Bland, for guidance in the preparation of this report, and to Dr. Louis Dienes, in whose laboratory the organisms were identified and the sensitivities and serum levels determined.

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Multiple Pulmonary Artery Aneurysms*

Endarteritis of Ductus Arteriosus and Congenital Pulmonary Cysts

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THE rarity of pulmonary artery aneurysm was cogently presented in the survey by Deterling and Clagett¹ which disclosed that eight cases of aneurysm were found in 109,571 necropsies gathered from various clinics both abroad and in this country for the period 1846 to 1946. Reports on congenital cysts of the lungs could not be found in American publications by Koontz² until 1925 when he reviewed foreign case reports and collected 108 cases, which aggregation also included allied conditions, such as diverticula of the trachea and bronchi, cysts of aberrant lung tissue, etc.

Necropsy reports on penicillin-treated patients with bacterial endocarditis are still scant. Since an unusual alliance of conditions, viz., widely patent ductus arteriosus with superimposed vegetative endarteritis, saccular aneurysm of the pulmonary artery stem, mycotic aneurysms of the peripheral pulmonary arterial radicles and congenital cyst formation in the lungs has been encountered in the same individual who in the latter part of her illness received intensive antibiotic therapy, the case is considered to be of enough interest to warrant reporting in some detail.

CASE REPORT

A seventeen year old white schoolgirl was admitted to the Peter Bent Brigham Hospital for the first time because of increasing weakness and fever.

The family history was without significance. The past history disclosed that the patient's birth and development were apparently normal except for a cardiac murmur first noted at six months and characterized as having the sound of a "threshing machine." There was no history

of rheumatic fever, scarlet fever or cyanosis. The usual childhood illnesses were experienced without complications.

Approximately seven months prior to admission the patient had an appendectomy performed following an episode of acute abdominal pain. Following the operation the details of which are unknown, the patient continued to feel "run down" but without specific complaints. She thought she had lost some weight during the four to five months prior to entry. About six weeks before admission to this hospital the patient had an upper respiratory infection accompanied by fever. Following treatment with sulfonamides, hematuria is alleged to have occurred; the medication was stopped. Because of persistent fever, the patient was admitted to another hospital. It is reported that "gamma streptococci" were grown from her blood on several occasions. One urine specimen was grossly bloody. During this period she was treated with penicillin in doses of 75 to 100,000 units every three hours; during the week before entry to this hospital she received 150,000 units of streptomycin every four hours. The fever did not subside and the patient had repeated episodes of what were considered to be pulmonary infarctions. The hemoglobin dropped to 40 per cent and rose only slightly with aid of a transfusion. She complained intermittently of pain between the shoulders and pain in the chest on inspiration.

Physical examination revealed the following: temperature, 102°F., pulse, 120; respirations, 24 and blood pressure 115/60. The patient was a poorly nourished, normally developed young white girl who appeared chronically ill and seemed to be in moderate distress. Her cheeks were flushed and there was slight labial cyanosis. There was slight facial asymmetry associated with torticollis. A single petechia was seen in the temporal field of each fundus. The heart was greatly enlarged to the left at both the

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apex and the base. P_2 was loud and snapping and of greater intensity than A_2 . There was a grade IV continuous murmur heard over the pulmonic area and upper precordium and through to the back. A grade III apical systolic murmur and a snapping mitral first sound were heard. The apical rate was 132 and regular. The inferior border of liver dullness was found to be 3 fingerbreadths below the right costal margin although the inferior liver edge was not palpated. The tip of the spleen was palpated 6 cm. below the left costal margin and was tender. The lungs were clear except for fine basal rales bilaterally. No peripheral edema was present. Moderate arachnodactyly was noted.

Laboratory data was as follows: A serologic test for syphilis (Hinton) was negative; the urine was concentrated to 1.033, there was persistent 1 to 3 plus proteinuria and red and white cells as well as a few granular casts were seen in all sediments. The erythrocyte sedimentation rate was consistently elevated. The hematocrit varied between 29 and 32 rising terminally to 40. The white blood cell count varied from 11 to 15,000 with a normal differential pattern. Routine blood chemistry values were within normal limits. Ten blood cultures and a sternal marrow culture yielded no growth. Nose and throat cultures revealed no significant flora. Blood penicillin levels varied between 5 to 20 units/cc. Electrocardiogram showed left axis deviation. Unipolar chest leads showed unusually high R waves in V_1 and V_2 and elevated S-T segments in V_2 and V_4 . The tracings suggested that the apex of the heart was displaced to the left and posteriorly. The rate was 125, P-R interval 0.16, QRS duration 0.09 seconds. Chest films on admission showed marked enlargement of all borders and the left auricle and ventricle particularly. Fluoroscopy showed a good, regular beat with pulsation of the hilar vessels. There was a marked degree of congestion. Two subsequent films showed increase in basal cloudiness with a trace of fluid at the right base. The venous pressure was 140 mm. of normal saline and the circulation time (magnesium sulfate) was 20 seconds.

The patient's fever persisted despite massive penicillin therapy started on the fifth hospital day. The dosage schedule was 4.8 million units which was increased to 9.6 million units from the eighth through the fourteenth hospital day and maintained at 4.8 million units from the

nineteenth through the twenty-ninth hospital day. She was fully digitalized. A surgical consultant was of the opinion that the patient was not in adequate condition for surgical interference. There was marked tachycardia and tachypnea. On the twelfth and fourteenth hospital days the patient had a series of brisk and copious hemoptyses associated with severe chest pain. She rallied fairly well from these episodes but the fever continued practically unabated. On the twenty-eighth hospital day she had gross hemoptysis again which recurred at frequent intervals, with the production of increasing quantities of blood. The patient expired on the thirtieth hospital day.

Autopsy was performed eleven hours postmortem; only the salient findings are described.

The cadaver was that of a well developed but poorly nourished young white female who appeared slightly younger than her stated age (seventeen). There was marked pallor of the mucosal and cutaneous surfaces but no petechiae were found. Upon opening the chest, 1,250 cc. of clotted blood were found in the left hemithorax, which had originated from a pleural rent overlying the anterolateral aspect of the left lower lobe; there was no excessive fluid in the right hemithorax.

There was 150 cc. of a slightly turbid, odorless, light green fluid in the pericardial sac which was lined by a smooth lustrous pericardium. The heart weighed 550 Gm. and was uniformly enlarged but not dilated. There were two "soldier spots" in the anterior epicardium of the right ventricle. The valves were all normal except for two glistening, grey, 3 mm. papules on the atrial surface of the posterior mitral leaflet about 2 mm. from the closure edge.

Microscopically, numerous sections of the ventricles, atria and auricular appendages revealed no typical rheumatic stigmas. A few focal areas of myocardial fibrosis were seen usually in relation to the coronary radicles. The "soldier spots" were produced by focal areas of fibrous connective tissue which was slightly hyalinized and with little cellular infiltration. The papular lesion of the posterior mitral leaflet comprised a center of edematous connective tissue in which fibroblasts, capillaries and some neutrophiles were seen; the core was surrounded by some fibrin which, in turn, was endothelialized. Examination of the mitral valve lesions stained with a modified Gram's stain failed to disclose any bacteria.

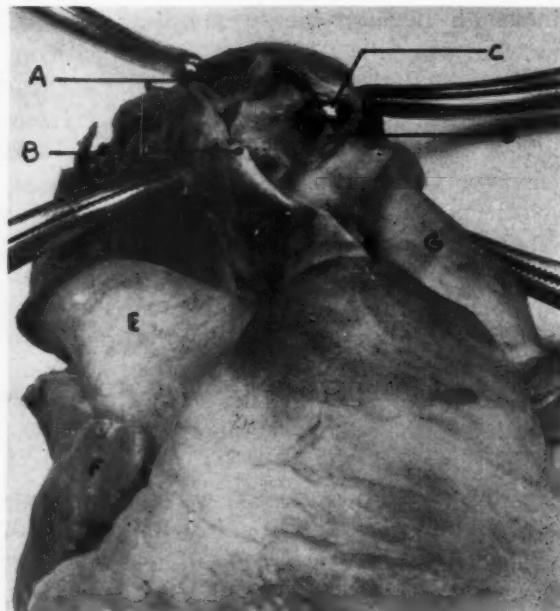


FIG. 1. Anterior aspect of heart with anterior half of pulmonary conus removed. A, clamp mark in fundus of saccular aneurysm; B, proximal margin of aneurysmal mouth showing abrupt loss of media (white); C, ductus arteriosus lumen; D, attachment site of ductal vegetation; E, aorta; F, right auricle; G, intima of pulmonary conus.

Approximately 5 cm. distal to the pulmonary valve ring there was a saccular aneurysm of the pulmonary trunk 0.8 cm. deep with a circular orifice having a diameter of 1.2 cm. (Fig. 1.) The intimal lining of the aneurysm was dull, red-grey and granular. In the area immediately proximal to the aneurysm the intima appeared pitted and reddened but with no evidence of frank ulceration. There was no evidence of media in the aneurysm and the surrounding adventitia was not unduly thickened. Approximately 0.5 cm. distal to the aneurysm the opening of the ductus arteriosus was seen; the latter was short but wide with respective dimensions of 0.3 by 0.6 cm.—virtually a side-by-side anastomosis between the aorta and pulmonary trunk. The ductus inserted into the aorta about 2.0 cm. distal to the origin of the left subclavian artery. An elongated, red-grey and granular vegetation was seen to arise at the pulmonary side of the ductus and extend through it with the free end presenting in the lumen of the aorta; the vegetation measured 0.3 by 0.2 by 0.6 cm. A similar vegetation, but smaller, was seen where the ductus inserted into the aorta. Neither vegetation was remarkably friable.

Microscopically, a section including relatively normal pulmonary artery trunk and the area of transition into aneurysm revealed focal as well



FIG. 2. Photomicrograph of pulmonary artery trunk immediately proximal to the saccular aneurysm showing the prototype of medial destruction. Weigert's elastic tissue stain; $\times 18$.

as diffuse hyalinization of the media. There were focal collections of lymphocytes in the media and adventitia. Macrophages containing hemosiderin were present both in the intima and media. Sections stained for elastic tissue by Weigert's method revealed disruption and irregular distribution of the elastic lamellae in the proximal pulmonary artery with complete absence of elastic fibers in the aneurysm. There was no remarkable alteration of the adventitia or *vasa vasorum*. Sections of the pulmonary artery proximal to the aneurysm which appeared grossly pitted and reddened disclosed miliary aneurysm formation, the histologic features of which were identical with those described previously. (Fig. 2.) Sections through the origin of the ductus revealed marked intimal proliferation and hyalinization of the pulmonary trunk proximal to the ductus; there was also disruption of the elastic lamellae as well as diminution in quantity. Lymphocytes were seen in the media. As the ductus was reached the appearance of the latter approached that of normal aorta. The ductus vegetation was constituted by a mass of blood cellular debris which was invaded at its base by fibroblasts and capillaries; the vegetation was not endothelialized. No bacteria were seen.

The most striking change was seen in the left lower lobe of the lung which was densely hemorrhagic, with a torn pleural membrane on its anterolateral aspect. (Fig. 3.) Multiple parallel sections were made and these revealed most of the lobe to be occupied by a large multilocular cystic structure lined by a dull grey membranous tissue in which laminated blood clot was present. As the pulmonary hilus was approached it was possible to demonstrate a communication



FIG. 3. Anterior aspect of lung; left lower lobe is cut sagittally revealing cystic appearance of hemorrhagic infarct. Note pleural rent and thickening.

between a radicle of the left lower pulmonary artery and the large hematoma. (Fig. 4.) The actual point of rupture could not be found in the face of the prodigious hemorrhagic infiltration. Communication of the hematoma with a comparably-sized bronchial radicle could not be demonstrated. Similar vascular changes were not seen elsewhere; there was no grossly evident vascular sclerosis. Additional findings in the lungs were: a multilocular cyst in the left upper lobe containing a thin, opalescent fluid which did not communicate with the bronchial tree (Fig. 5); a unilocular cyst in the right lower lobe containing a small blood clot; a recent small infarct of the right middle lobe.

Microscopically, the histologic picture was difficult to interpret because of the intense hemorrhagic infiltration. However, sections stained for elastic tissue by Weigert's method helped to delineate the various architectural features. The lining of the cystic space in the left lower lobe was devoid of epithelium and constituted by a laminated fibrous connective tissue and intimately adherent to the adjacent blood clot which was invaded by fibroblasts and capillaries. Near the fibrous cyst wall there was a small-sized artery which arrested attention by virtue of almost complete loss of internal elastic membrane and media with eccentric dilatation of the vessel wall; the proliferated intima appeared to be apposed to the adventitia in much the same manner as was seen in the large

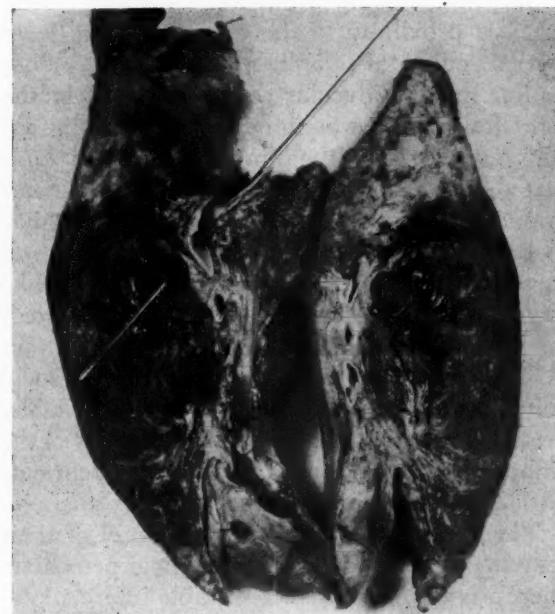


FIG. 4. Sagittal surfaces of left lower lobe; the probe passes through a left lower pulmonary arterial radicle into the hemorrhagic infarct.

saccular aneurysm. (Fig. 6.) The medium-sized arterial radicle seen in the gross specimen to communicate with the hematomatous cyst could not be positively identified in the microscopic preparations. In addition to this vascular medial change a second deviation from the normal was that of an obliterative intimal proliferation; the latter change was found in all lobes. The multilocular cyst of the left upper lobe was lined by a

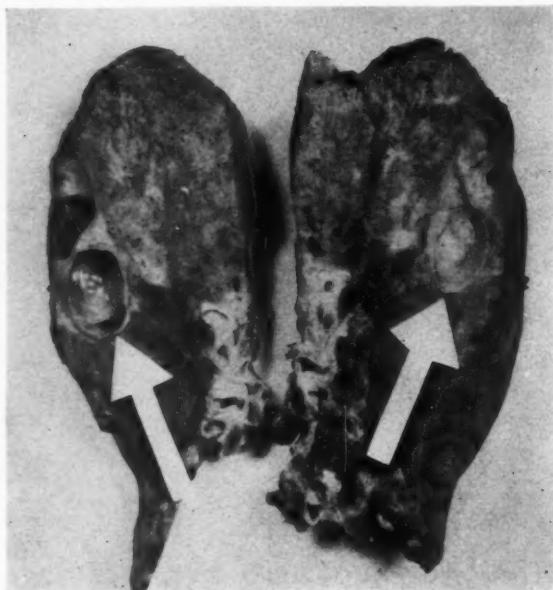


FIG. 5. Multilocular cysts of left upper lobe.

discontinuous epithelium; the epithelial cells were flattened and cuboidal with poor cellular outline and vaguely reminiscent of a syncytium. In close proximity to the cyst wall there were several cuboidal-cell lined spaces somewhat similar to tubo-alveolar ducts. The cyst in the right lower lobe was lined by a discontinuous columnar type epithelium resting on a laminated, fibrous tissue without a definitive membrane propria; the morphology was very similar to bronchial epithelium. Beneath the cyst wall there were several collapsed bronchiallike structures with cartilagenous plaques interposed. In addition the cyst wall was seen to contain hemosiderin-laden macrophages and a few focal collections of lymphocytes. There were many areas of fibrous scarring in other sections of the right lower lobe consistent with the appearance of old, healed pulmonary infarcts.

The kidneys were striking by virtue of their extreme pallor and scattered cortical petechiae; there were no grossly recognizable infarcts.

Microscopically, the dominant lesion was glomerular and consisted of focal to complete hyalinization of the capillary tuft. There was periglomerular lymphocytic infiltration with no evidence of an acute exudative reaction.

The spleen weighed 280 Gm. and was not further remarkable; there were no infarcts grossly or microscopically.

Cultures from the pleural spaces, pericardial cavity, heart blood and lungs yielded no growth. The ductal vegetation was removed with sterile

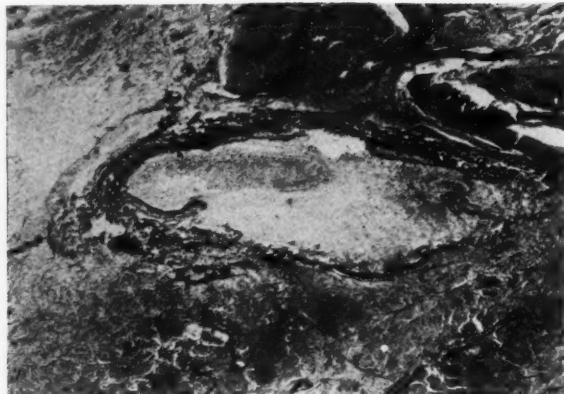


FIG. 6. Photomicrograph of arterial lesion in left lower lobe; note intimal proliferation and loss of media with eccentric dilatation. Weigert's elastic tissue stain; $\times 20$.

precautions, ground in a mortar and incubated in appropriate media for two weeks with no growth observed. The mitral valve papules were smeared and the swabs incubated; no growth was obtained.

Final anatomic diagnoses were: Hemothorax, left; mycotic aneurysms of the peripheral pulmonary arterial radicles; ductus arteriosus with vegetative endarteritis; saccular (mycotic) aneurysm of the pulmonary artery trunk; non-bacterial mitral valvulitis; pulmonary infarcts, recent and old, bilateral; congenital cysts of lungs; focal embolic glomerulonephritis.

COMMENT

Aneurysm Formation in the Pulmonary Vascular Tree. Brenner³ observed that saccular aneurysm formation of the pulmonary artery stem and main branches was exceedingly rare, fusiform dilatation being much more common. He offered the following etiologic classification of pulmonary artery aneurysm formation: 1) Traumatic, rare. 2) Mycotic, aneurysm formation in association with infection of a congenital cardiac defect. 3) Congenital, associated with congenital cardiac defects which are not demonstrably infected but in which weakness of the arterial wall was probably due to congenital deficiency in elastic tissue. 4) Syphilitic, with typical mesarteritis and the demonstration by Warthin⁴ of spirochetes in the media. Excepting Warthin's work, unequivocal demonstration of the pathogenesis of pulmonary artery aneurysm is rarely if ever made. The Boyd and McGavack⁵ survey of

139 cases of pulmonary artery aneurysm indicated syphilis to be a significant factor in only 31.7 per cent of the cases. Deterling and Clagett¹ in a later review of thirty-six cases which they collected showed a comparable incidence of 39 per cent. In the case herein presented there was no historical, clinical or laboratory evidence implicating luetic infection as an etiologic factor.

With regard to the mechanism of mycotic aneurysm formation, Brenner has postulated these pathways: (1) spread by continuity from infective endocarditis of the pulmonary valve; (2) invasion from without by spread from an infective process in the surrounding tissues; (3) invasion through the *vasa vasorum*; (4) infection reaching the pulmonary vessels from the lumen by means of an infected embolus or the direct implantation of infection in the intima without preceding embolism. The saccular aneurysm described earlier cannot be definitely classed as mycotic or congenital exclusively; both factors may have been involved. The occurrence of a vegetative endarteritis in association with a ductus arteriosus suggests that the aneurysm resulted from the interplay of such factors as infection of the arterial wall and pressure of blood reflux through the ductus although congenital deficiency of elastic fibers cannot be ruled out. The morphology of the aneurysm with the abrupt change in disposition of the elastic lamellae not associated with the bifurcation of a vessel is more strongly in favor of the acquired nature of the lesion. The proximity of the saccular aneurysm and the site of the ductal vegetation indicates that infection by direct contiguity was the likely avenue of infection.

The histologic identification of the peripheral pulmonary arterial radicle which communicated with the hematomatous cyst of the left lower lobe was not possible because of the situation of the lesion in a markedly hemorrhagic tissue. Yet demonstration of the medial disease in smaller-sized vessels in the immediate area of the larger artery which was histologically comparable to the saccular aneurysm of the pulmonary artery

stem inevitably directs to the conclusion that similar changes occurred in the larger radicle.

Another factor which has been considered in the genesis of aneurysm formation in the pulmonary tree is that of atherosclerosis. Deterling and Clagett described the presence of atherosclerosis in the right pulmonary artery (site of aneurysm) and microscopically in the arterioles of both lungs in their case. In view of Brenner's finding of arteriosclerosis microscopically in the pulmonary vessels in 97 per cent of one hundred consecutive unselected autopsy cases (a group which included some children) the exact position of atherosclerosis in a cause-effect relationship with pulmonary artery aneurysm formation is somewhat obscure.

The absence of any anatomic evidence of pulmonary tuberculosis serves to exclude the possibility of a Rasmussen aneurysm—an aneurysm in the wall of a tuberculous cavity and an important cause of the brisk hemoptysis seen in clinical pulmonary tuberculosis.

Cyst Formation in the Lungs. The multiple pulmonary cysts encountered in the case reported which were found to be lined by a variegated epithelium or none at all in the absence of demonstrable bronchial disease or other parenchymal affection (excepting infarct) hints very strongly to their congenital nature. To be sure the determination of the nature of a pulmonary cyst in the adult is almost never definitive, as Koontz pointed out. The difficulties are such that the validity of the concept of congenital cystic formation in the lungs has been questioned by some; certainly there is far from unanimity of opinion regarding the etiologic factors in certain pulmonary cystic structures. Be that as it may, the process appears to occur more frequently than was considered at the time Koontz published his report on congenital cysts of the lungs. Thus, in the decade following Koontz' paper, King and Harris⁶ collected 152 cases of cystic formation in the lungs. Additional papers on this subject have been published by

Schenck,⁷ Smith,⁸ Stanford and Nalle⁹ and Ruschin.¹⁰

Cysts of the lungs of established etiology, e.g., hydatid, dermoid, bronchiectatic, etc., should not be confused with the congenital variety. Koontz cited the following terms used synonymously: fetal bronchiectasis, congenital cystic formation of the lungs, atelectatic bronchiectasis, congenital bronchiectasis, honeycomb lungs, etc.; he concluded from the foregoing that the varied nomenclature depended on the pathogenetic interpretations of the various investigators. King and Harris believed that the condition resulted from an anomaly which interrupts the canalization of a ramification of the embryonic bronchial radicle leading to obstruction of the distal portion of the pulmonary buds which develop more completely. There being no bronchial outlet the accumulated secretions then distend the space they are formed in which results in encroachment and compression of the surrounding pulmonary tissue. Norris and Tyson¹¹ studied polycystic disease in two infants by means of numerous serial sections and compared them with polycystic disease of the kidney, liver and pancreas; they concluded that ". . . polycystic disease is a pathologic manifestation of normal fetal resorption and degeneration."

The cyst wall is constituted of an epithelial layer made up of columnar cells with or without cilia, cuboidal cells, flattened cells or no epithelium at all with bare connective tissue forming the lining. Koontz believed that the lack of pigment in the congenital lesions indicates that the affected part had never functioned and that therefore the pathologic condition antedated birth. Ruschin pointed out that the occurrence of pulmonary cysts in the stillborn and newborn as proved by autopsy is probably the strongest evidence in favor of the congenital nature of this disorder.

Thus, in the absence of any demonstrable cause for the acquired nature of the pulmonary cysts in this case, their congenital origin is implied.

Effects of Penicillin on the Course of Bacterial

Endocarditis. The finding of a sterile vegetation which appeared to be well organized and the absence of an exudative reaction in the vascular lesions (including the glomeruli) is in accord with the observations of recent investigators, Geiger and Durlacher¹² and Moore.¹³ This writer agrees with Geiger and Durlacher who believe that the infectious component of bacterial endocarditis is eradicable with penicillin.

The reconstruction of events as they occurred in the case reported herein appears to be as follows: Vegetative endarteritis developed at the mouth of the ductus arteriosus in the wake of the episode of acute appendicitis which was treated by appendectomy. This lesion served as the nidus for the subsequent dissemination of infectious emboli and bacteria which ultimately caused the vascular disease manifested by aneurysm formation, pulmonary infarctions and focal embolic glomerulonephritis. That the infectious process was eventually controlled—but too late—by intensive antibiotic therapy is suggested by the absence of acute inflammatory and minimal presence of chronic inflammatory reaction in the vascular lesions, the lack of exudative reaction in the kidneys, the sterility of the ductal vegetation and the absence of bacteria in histologic preparations of the latter. Ordinarily pulmonary infarcts do not rupture through the visceral pleural membrane; however, such a development did occur in this patient and caused fatal hemothorax. The occurrence of pulmonary cysts in the right lower and left upper lobes suggests that similar cysts in the left lower lobe confronted with the mass of an expanding hematoma caused by a mycotic aneurysm could not maintain their integrity and ruptured, the sanguineous homologue of spontaneous pneumothorax resulting from the rupture of a subpleural bulla.

SUMMARY

A case is described in which multiple mycotic pulmonary artery aneurysms were found in association with vegetative endarteritis of a widely patent ductus arteriosus;

there were concomitant congenital pulmonary cysts. Death resulted from rupture of a peripheral pulmonary arterial branch producing a large hemothorax.

In view of the massive penicillin therapy administered to the patient the histopathologic appearance of the vascular and visceral lesions suggests that the infectious element of bacterial endocarditis was eradicable by use of appropriate antibiotics.

An interpretation of the clinicopathologic sequence of events is offered.

Acknowledgment: The writer wishes to acknowledge the criticism and counsel given by Dr. Alan R. Moritz, Pathologist-in-Chief to the Peter Bent Brigham Hospital, in the preparation of this report.

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Relapsing Febrile Non-suppurative Panniculitis*

(*Weber-Christian Disease*)

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DESPITE the fact that Weber-Christian disease is considered rare, we have seen two cases within a period of two months. In this paper we will discuss the pathologic and clinical findings in these patients. Treatment will be described and an attempt will be made to evaluate an apparent etiology.

Since the first report of this pathologic entity was made in 1892 by Pfeifer,¹ approximately thirty-one cases have been cited. A complete review of the cases to 1943 was made by Miller and Kritzler.² This article is significant, too, in that it reports the first autopsy of a patient with acute lesions of Weber-Christian disease. The autopsy findings revealed focal necrosis and fatty changes in the liver, hydropic degeneration of adrenal cortex cells and large numbers of red cells in the fixed members of the reticuloendothelial system. Possible etiologies of the disease were considered as follows: (1) iodides and bromides; (2) foci of infection; (3) avitaminosis. However, the authors believe that because sulfonamide compounds failed to affect the disease, its infectious origin is doubtful.

The second autopsy findings reported by Spain and Foley³ showed fatty changes in the viscera. Necrotic areas in the mesenteric, omental and pretracheal fat were noted, as well as necrotic areas in the subcutaneous fat. In this case the patient developed nodules after having been hospitalized for

uremia of which he subsequently died. Examination of the kidneys disclosed end stages of chronic glomerulonephritis.

Various methods of treatment have been suggested for this disease. Arnold⁴ used sulfadiazine and sulfathiazole without results in a patient who showed severe vascular damage in the nodules. However, he found that the patient responded to sulfapyridine. On five occasions sulfapyridine was withheld and relapses followed. During each relapse this patient had an elevation of the sedimentation rate. Each time the drug was resumed remission ensued within twenty-four hours.

Zee's⁵ patient with leukopenia was treated with sulfadiazine without apparent effect. He tried penicillin and his report is the first one of panniculitis treated with this drug. A total of 2,360,000 units was given. After three and one-half months following cessation of the treatment there was no recurrence of lesions or symptoms.

The case of the most marked leukopenia was described by Friedman.⁶ He found no elevation in the sedimentation rate. His patient had panniculitis for five years previous to her death; she died of staphylococcal septicemia after removing a crusted "keratosis" with a razor.

One patient with Weber-Christian disease whose case was reviewed by Larkin et al.⁷ recovered spontaneously after six months. However, the case in the literature which

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showed the most generalized involvement proved fatal to the patient. This case was reported by Mostofi and Engleman.⁸ Although the patient in this instance had a normal sedimentation rate and negative blood cultures, recurrent fever was present over a period of seven months, during the last two months of which the cutaneous lesions had appeared. The patient received sulfadiazine and penicillin without effect.

Following are the reports of two cases; one of the patients was treated with penicillin and streptomycin. As far as we know this is the first patient with panniculitis treated with streptomycin.

CASE REPORTS

CASE 1. The patient was a thirty-two year old, white housewife who came to the female medicine clinic complaining of outbreaks of subcutaneous nodules over a two and one-half-year period. Her family history revealed that her mother died of a pulmonary embolism three months after childbirth. The patient's father has rheumatism, heart trouble and had profuse bleeding at the time of extraction of his teeth. One sister was a blue baby who died soon after birth; one aunt died of pulmonary tuberculosis. One sister and two brothers are living and well. The previous personal history showed that the patient had the usual childhood diseases and frequent epistaxis, the last episode occurring at the age of twenty-one. Onset of the menarche was at eleven years of age and the periods have been normal. A history of chronic constipation was noted for which the patient took various laxatives and mineral oil. In 1944, for a period of one year, she took approximately two tablets of alkaseltzer every two or three days because of a "sour stomach" after eating.

Previous nodules and blisters were described by the patient. Since 1935 she noticed that she bruised easily and occasionally a nodule formed in an ecchymotic area. In 1943, while working in a plant dehydrating carrots and occasionally cabbage, she had an attack of "itching water blisters" on her legs, abdomen, hips and arms. A physician at that time diagnosed the complaint as "carrot poison."

This patient's present illness began two and one-half years ago with outbreaks of subcu-

taneous nodules which were painful. The overlying skin was red. Since the onset, the patient has never been free of some nodules, each persisting about four to five days. However, a few larger ones persisted for about two to three weeks before disappearing and these left a tan tint to the skin for a few months. No pattern of distribution was found by the patient as nodules appeared practically all over her body.

No chills accompanied the nodules although at times the patient felt warm. Nevertheless, she did not take her temperature until instructed to do so at the clinic. She then discovered that she had a low grade fever on several occasions. This was two and one-half weeks before her hospital admission.

Physical examination was essentially negative except for mild obesity and a few scattered subcutaneous nodules over the lower extremities. These nodules were firm, moderately tender, and about 2 to 3 cm. in diameter. The nodules were not attached to the overlying skin which was slightly red. No pattern of distribution was seen.

Initial laboratory studies revealed an erythrocyte count of 3,500,000; hemoglobin was 13 Gm. and there was a leukocyte count of 7,400, with 72 neutrophil and 28 lymphocytes. Sedimentation rate was 3 mm. in one hour (Wintrobe). Blood Kahn was negative; blood culture showed no growth after one week and the urine was normal.

A biopsy of a nodule of the left leg was taken and sent to the Fifteenth Histopathologic Center, Brooke General Hospital. The specimen was diagnosed as an acute non-suppurative panniculitis. The description of the microscopic section was as follows: "The specimen consists of fatty tissue, which is infiltrated with large numbers of neutrophiles and a few eosinophiles. There is likewise considerable hemorrhage and the blood vessels in the fat are engorged. In one region there is a large collection of neutrophiles and red blood cells resembling a micro-abscess." The biopsy wound failed to heal for about two and one-half weeks. No apparent infection was visible. (Fig. 1.)

Then a second biopsy was made of a nodule of the left leg and the specimen sent to Brooke General Hospital. The diagnosis again was acute non-suppurative panniculitis. "The pathological picture in this case is essentially similar to that described in the previous biopsy. The clinical history and pathological findings in this case

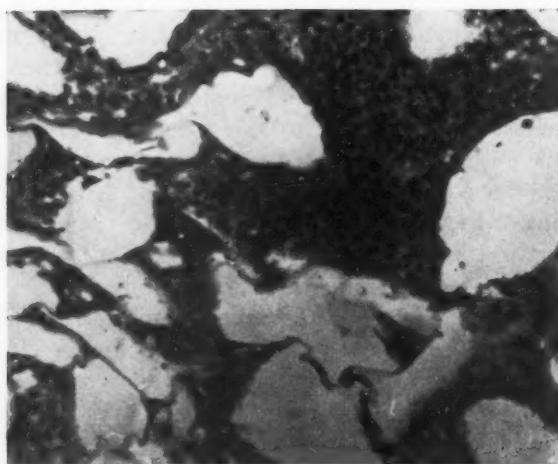


FIG. 1. Photomicrograph of section from nodule of left leg of Case 1 showing fatty tissue with large number of neutrophils.

are thought to be consistent with a diagnosis of Weber-Christian disease. In this case, however, the acute inflammatory elements are much greater than in those reported in the literature.⁵ This second biopsy wound took about three weeks to heal, during which time there was a thin, yellow, apparently non-purulent drainage.

On August 27, 1947, the patient was admitted to Camp Hood Station Hospital for treatment with penicillin, as suggested in a previous favorable report.⁵ On August 28th, 30,000 units of penicillin were started intramuscularly every three hours. The temperature became normal soon after the start of the drug. The nodules became fewer in number and lasted about one day whereas they had previously lasted four to five days. Dental and ear, nose and throat examinations at this time failed to reveal any focus of infection. An electrocardiogram was within normal limits. A barium enema was negative of results. The basal metabolic rate was plus 1 and the blood cholesterol was 287 mg. per cent. On September 17th penicillin was discontinued after the patient had received 4,600,000 units over a period of eighteen days. Attention is called to the fact that this is twice the amount given by Zee. It was believed that in our patients there was marked improvement but not a complete cure.

Because the patient was not entirely cured, on September 17th, 0.5 Gm. of streptomycin was given intramuscularly every three hours. On September 19th the temperature went up to 100.4°F. (oral) and on September 20th to 101.6°F. (oral). The same day an indurated area was noticed on the right upper arm at the

site of a previous streptomycin injection. After this the patient began having aching pains in her elbows, hips and knees although no swelling of the joints was visible. On September 21st streptomycin was discontinued due to toxic reactions and the patient received benadryl instead. The patient continued to have a temperature up to 101°F. (oral) daily until the 24th, and then the temperature dropped to normal. Between the end of streptomycin injections and the return to normal of the patient's temperature (a period of three days) the patient developed nodules on the buttocks where she had received the streptomycin. These nodules appeared larger and more tender than any previous ones. Examination of two blood cultures was negative. The patient's white blood count went up to 17,600 and 19,000, respectively, with a shift to the left during elevation of temperature.

On September 30th, six days after the temperature was normal, 0.25 Gm. of streptomycin was started again and was given intramuscularly every three hours. On October 2nd the patient began having aching pains in both knees. On October 3rd she developed an area of anesthesia over the anterior surface of the left thigh, 5 cm. by 3 cm. The drug was discontinued again because of toxic reactions, after the patient had received 23 Gm. *in toto*. On October 4th she developed mild tinnitus.

The patient continued to get an occasional small subcutaneous nodule on one of the extremities. Her temperature went up to 99.8°F. (oral) on the 6th and to 100.2°F. (oral) on October 7th; there were chills. The temperature then returned to normal. This time the patient developed many large tender indurated masses on her thighs where she had received streptomycin. On October 13th one of the masses felt cystic and it was aspirated. Purulent material, over which a layer of fatty material floated, was found. Following aspiration the patient decided to return to her home in the northwest and she will be followed subsequently in the medical clinic.

CASE II. The patient was a twenty-eight year old white woman who considered herself to be in good health until 1939 when she first noted the occurrence of red areas on the anterior aspects of both legs. These lesions were acutely tender, they varied in size from 3 to 4 mm. to 5 or 6 cm. in diameter and were noted to disappear in two to three weeks with concomitant occurrence of new lesions. There have been as

many as fifty or sixty lesions at the same time and as few as three or four. The nodules were subcutaneous and not fixed to the skin. There was no scarring or depression of the skin manifested clinically when the lesions disappeared. The first episode lasted approximately four months and the patient spontaneously became asymptomatic. Since that time, the patient has had five such episodes lasting three to four months, each of which has occurred about every two to three years. The patient believes that she has had fever with each appearance of the nodules and frequently in the intervals between these episodes.

Since 1943, the patient has had recurrent episodes of joint pain which are limited to the hip, knee and ankle joints. The pain is sudden in onset and is not accompanied by swelling or redness although there is tenderness in the involved joints. The pain is migratory and ceases as promptly as it appears. It has lasted from a few hours to twenty-five or thirty days. This symptom has occurred both independently and in association with the subcutaneous nodules. A diagnosis of rheumatic fever was made in another hospital in July, 1946. At this time the patient had a severe attack characterized by fifty to sixty acutely tender, inflamed, subcutaneous nodules limited to the lower extremities. A biopsy was not made at this time.

The past medical history disclosed that the patient has had severe, recurrent sore throats all her life, characterized by fever, dysphagia, generalized aching, malaise and slow convalescence. She complained of dyspnea on mild exertion since 1942. There was rather marked fatigue and slowly progressive asthenia. No familial or environmental factors were elicited. The patient has had two normal, uneventful pregnancies.

The patient was a well developed, well nourished white female. The thyroid gland was moderately and diffusely enlarged. The ocular fundi were normal. Her lung fields were clinically normal. Examination of the heart disclosed a short, high-pitched systolic murmur in the fourth interspace to the left of the sternum. The second pulmonary sound was of greater intensity than the aortic. There were several red, tender areas about both knees. These were subcutaneous nodules not fixed to the skin, and they varied in size from 3 mm. to 3 cm. in diameter. The peripheral pulses were normal. The temperature was 99.4°F. (oral).

Blood count revealed 4,300,000 erythrocytes; 13.0 Gm. hemoglobin; 7,650 leukocytes with 56 per cent polymorphonuclear cells and 44 per cent lymphocytes. Repeated counts were essentially the same and the blood Kahn was negative. All urinalyses were normal. Blood chemistry studies, including a blood urea nitrogen, fasting blood sugar, serum cholesterol and total serum proteins, were normal. The sedimentation rate varied from 9 mm. to 18 mm. (Wintrobe). Examination of two blood cultures was negative. Basal metabolic rate was plus 5. X-ray films of the chest, knees and ankles were interpreted as normal.

Serial electrocardiograms recorded during severe tonsillitis and pharyngitis have demonstrated a P-R interval of .22 seconds, flat T₂ and inverted T₃ and T₄, with a deviation of the electrical axis to the left and low voltage QRS complexes. The tracings have been interpreted as representing the lowest grade of atrioventricular block and evidence of an existing myocarditis secondary to the tonsillitis. One month later the P-R interval was .18 seconds but low QRS complexes persisted. The patient received a total of 1,620,000 units of penicillin intramuscularly, using 30,000 units at three-hourly intervals as treatment for the tonsillitis. Streptococci were not found in repeated throat cultures.

Biopsies were obtained of one small nodule of one week's duration and of another that had been present for two months. Microscopically, the first specimen "consists of a fibrous and adipose tissue, in one region of which are a considerable number of macrophages with a pale-staining, foamy cytoplasm. In addition, there are considerable numbers of lymphocytes and a few eosinophiles and plasma cells. These appear to be in greatest concentration along the fibrous septae of the fat. In one of the fibrous septa a small blood vessel is cut in longitudinal section, and a considerable number of inflammatory cells are around this, also." The second specimen "consists of a fibrous and adipose tissue, in which there is a much greater degree of fat necrosis and inflammatory cell involvement than in the previous section. Many giant cells are seen, with peripherally-placed nuclei. Many macrophages with a pale, foamy cytoplasm are seen, and in addition, there are large numbers of lymphocytes and lesser numbers of eosinophiles and plasma cells." (Fig. 2.)

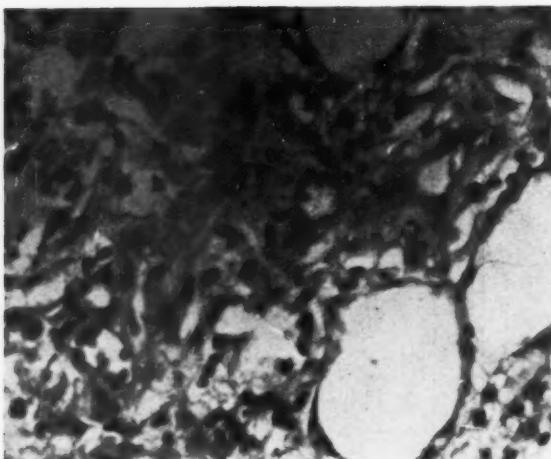


FIG. 2. Photomicrograph of section from nodule of leg of Case II showing a considerable number of macrophages, lymphocytes and a few eosinophiles and plasma cells.

The present episode is of three months' duration and the patient has continued to have three to five nodules continuously, with new lesions appearing as the older ones disappear. The patient has refused any further therapy but is seen periodically in the medical clinic.

COMMENTS AND CONCLUSIONS

The cases herein described conform, we believe, to the clinical and histologic criteria ascribed to Weber-Christian disease. From our study of this disease in our patients and in the literature we believe we are justified in drawing the following conclusions:

The first conclusion concerns the etiology of this disease. In the literature causes have been postulated as follows: (1) iodides and bromides; (2) foci of infection; (3) avitaminosis; (4) disturbance of fat metabolism; (5) undetermined specific infectious process and (6) bacterial allergy. Our cases seem to fall into the category of infectious process of

undetermined origin. Support of this etiology is shown by the apparent response of Case I to penicillin. This drug effected a return to normal temperature and a decrease in the number and size of the nodules. The fact that Case II failed to show a response can probably be attributed to the small dosage of the drug given and to the patient's refusal of further treatment.

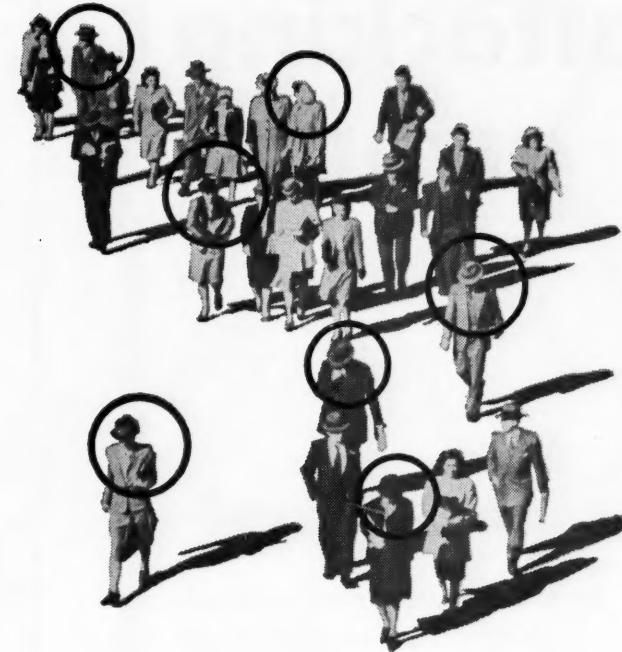
Second, we believe that the dosage of streptomycin was probably sufficient to prove that it was non-effective. As was described, this drug caused no changes in the nodules.

Third, we conclude that this disease may become generalized, occurring wherever fatty tissue is present. Support of this conclusion is found in the autopsy reports of Spain and Foley³ and Mostofi and Engleman.⁸

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*Nuzum, F. R.: In Diseases of the Digestive System, ed. by S. A. Portis, Lea & Febiger, 1944.

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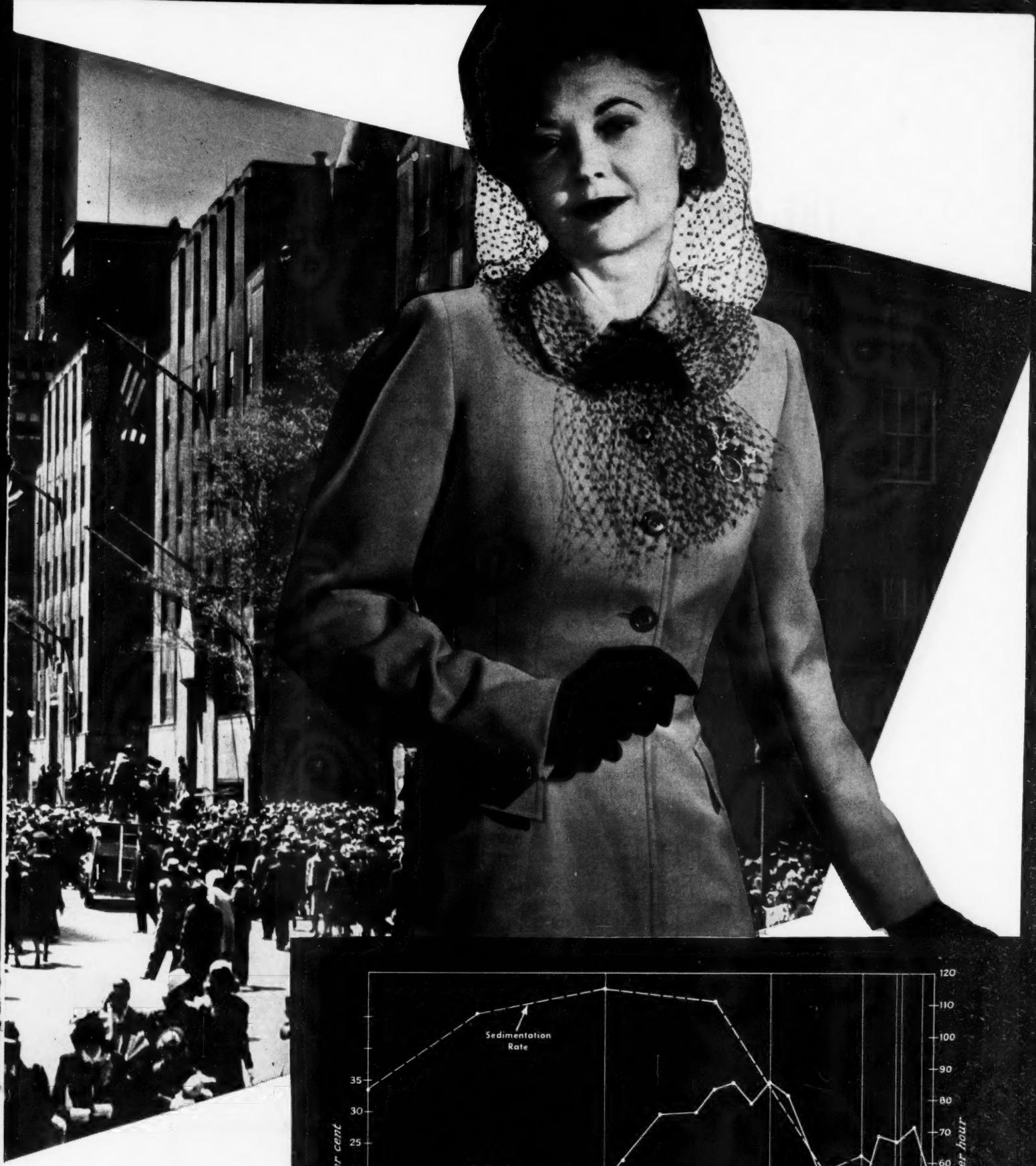
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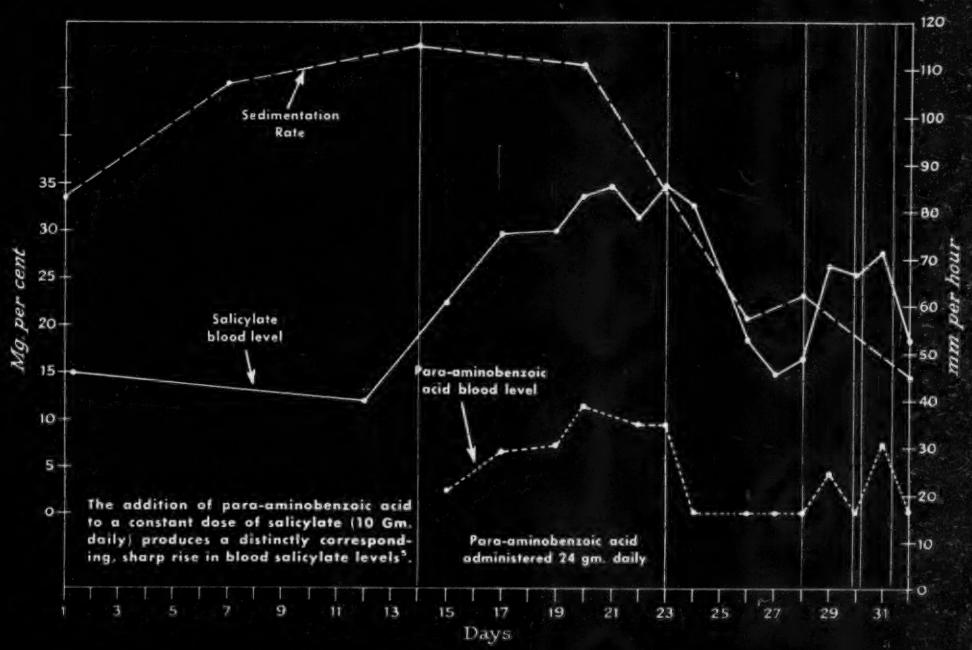
Salicylate blood level (in mg. per 100 cc.)	Erythrocyte sedimentation rate
less than 20 mg	no fall
20-30 mg	slow fall
30-40 mg	RETURN TO NORMAL, CLINICAL SYMPTOMS SUBSIDE





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1. Brewster, J. M., U. S. Naval Med. Bull. **49**: 1-11, January-February 1949.

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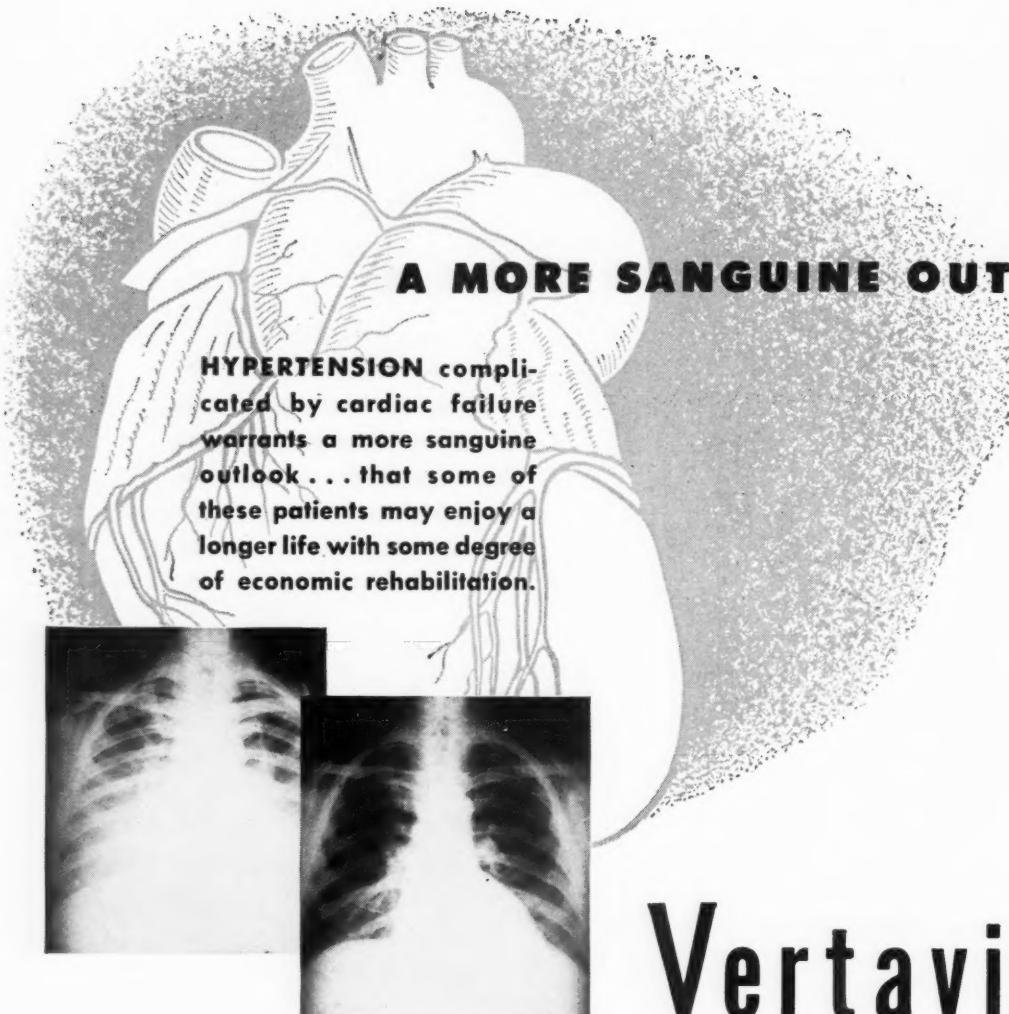
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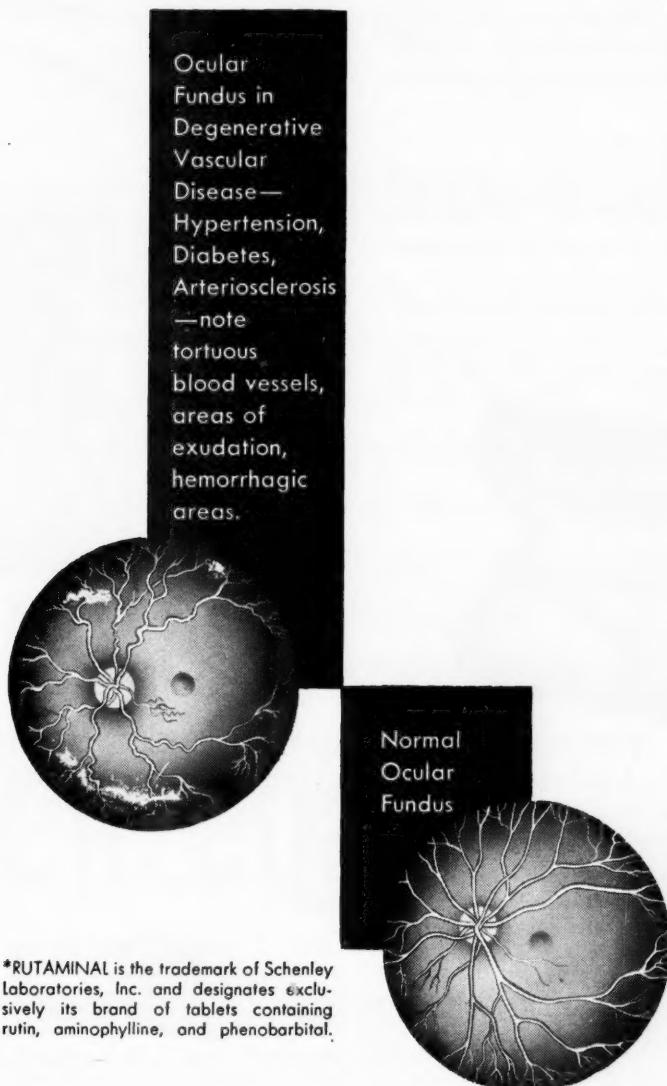
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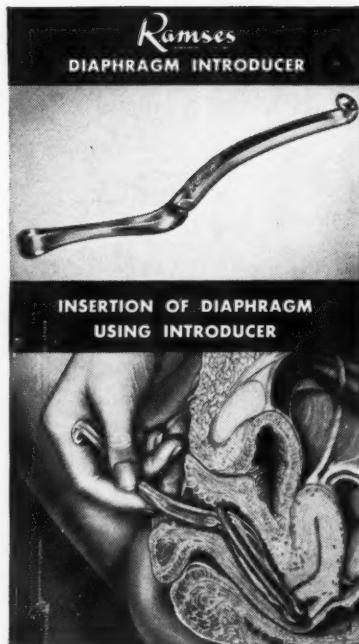
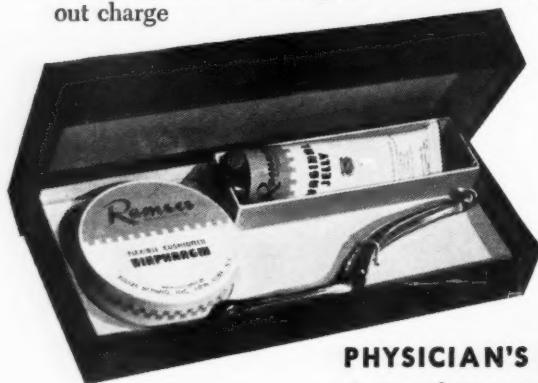
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